THE JOURNAL

OF THE

American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 171, NO. 9 — CHICAGO, ILLINOIS — OCTOBER 31, 1959

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STUDIES ON LIVE POLIOVIRUS VACCINE

ITS NEUROTROPIC ACTIVITY IN MONKEYS AND ITS INCREASED NEUROVIRULENCE AFTER MULTIPLICATION IN VACCINATED CHILDREN

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Comparative tests of the monkey neurovirulence of the Lederle-Cox and the Sabin strains of poliovirus, which are candidates for an orally administered vaccine, have indicated that children have been fed poliovirus strains possessing greater neurotropic activity than had been suspected. There was also evidence that, in passing through human hosts, some of the vaccine strains underwent genetic changes with respect to at least two properties in tissue culture, namely, the capacity to grow at 40 C (T marker) and the capacity to grow at low bicarbonate concentration (d marker). These changes after human passage were associated with increases in monkey neurovirulence. A further study of 596 postvaccination fecal specimens revealed that marked, though not complete, interference occurred between the vaccine virus and the enteroviruses already circulating in the population. This interference affected adversely the formation of the desired antibodies. It has not been proved that the strains used as orally given vaccine are dangerous either for the vaccinated child or for the community, but caution is called for, especially in view of the genetic instability of the attenuated strains of poliovirus currently available.

THE problems of the neurovirulence, genetic stability, and immunizing capacity of live poliovirus vaccines have been brought into sharper focus by the large-scale trials being conducted in different parts of the globe, as recently reported before the Pan American Health Organization–World Health Organization (PAHO-WHO) Conference on Live Poliovirus Vaccine held in Washington, D. C., during the week of June 22-26, 1959. We are summarizing here the results of our recent work on (1) comparative tests of the monkey neurovirulence of the Lederle-Cox strains and the Sabin strains being used as orally given vaccine, (2) the use of the *d* and *T* markers in tissue culture for determining genetic changes in attenuated poliovirus, (3) the correlation between genetic instability and increase in neurovirulence of strains after multiplication in the human alimentary tract, and (4) the limited immunizing capacity of attenuated poliovirus in an area with a high rate of enterovirus infection, presumably due to interference by the latter.

In addition, we would call attention to the fact that the feeding of a large number of persons does not, by itself, constitute an adequate safety test. Two questions must be asked in each field trial: 1. What percentage of those fed had already been immunized by prior natural exposure to poliovirus or by Salk vaccination? 2. Is there a significant difference in the number of cases of poliomyelitis among the vaccinated susceptible persons and their community contacts as compared with the number

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of cases which might have been expected had the same population been exposed to a virulent strain of virus? Some data illustrating this approach will also be discussed.

Materials and Method

Monkey Neurovirulence of Vaccine Strains.—Strains were made available through the kindness of Drs. A. B. Sabin and H. R. Cox. They were transported on Dry Ice and kept frozen until the day they were thawed and titrated in monkeys and in monkey-kidney cultures. From 22 to 26 monkeys were used for titrating each strain intracerebrally (IC) and from 22 to 43 for each strain intraspinally (IS). The IC dose was 1 ml. into the thalamus, with use of a 22-gauge needle; the IS dose was 0.1 ml. inoculated into the lumbar cord through the first intervertebral space below the last rib, with use of a 27-gauge needle. The latter was used in order to retain as much as possible of the 0.1-ml. inoculum in the lumbar cord. As a measure of a proper inoculation we sought to obtain continuous reflex contractions of the leg muscles during the inoculation. In order to achieve this, it was necessary, in many monkeys, to change the location of the needle during the course of injecting the vaccine.

After a period of observation of about four weeks, or less if the monkey was severely paralyzed, the animals were sacrificed and 30 sections of spinal cord were examined, 10 each from the cervical, thoracic, and lumbar areas. Lesions were graded from 1+ to 4+, a maximum score for both hemisections of one level being 8 (gross destruction of nerve cells plus extensive areas of cellular infiltration and perivascular cuffing); thus, the maximum score for the lumbar or cervical area of a monkey would be 80.

The data in tables 1 to 4 are a condensed summary of the titrations in about 400 young cynomolgus monkeys with a range of body weight of from 3 to 5 lb. (1.5 to 2.5 kg.). Each of the strains gave titers in the same range in monkey-kidney cultures, $10^{6.9}$ to $10^{7.5}$ tissue culture doses (TCD_{50}) per milliliter, similar to the results reported by Sabin and by Cox. However, marked differences were found between our results in monkeys and those reported by them.

For type 1, the Lederle material contained more than 300 monkey poliomyelitis doses (MPD_{50}) per milliliter by the IC route, and 300,000 MPD_{50} by the IS route (tables 1 and 4), MPD_{50} indicating the dose which produced specific lesions of poliomyelitis in 50% of the inoculated monkeys. (Usually, as shown in table 1, the titer based on lesions was about 0.5 to 1.0 $\log_{10}$ units higher than that based on the appearance of paralysis and weakness.) Sabin's strain produced a significant response in only two monkeys by the IC route, but the IS titer proved to be 100,000 MPD_{50} per milliliter. The extent of multiplication is also evidenced by the lesion scores presented in table 4. After IC injection, Lederle's strain produced marked destruction

TABLE 1.—*Comparative Titrations for Neurovirulence of Type 1 Candidates for Orally Given Poliovirus Vaccine**

Route of Inoculation	Concentration of Tissue-Culture Fluid	Monkeys Which Received Lederle-Cox Strain: Developing Weakness or Paralysis of Poliomyelitis†	Monkeys Which Received Lederle-Cox Strain: Developing Cord Lesions of Poliomyelitis	Monkeys Which Received Sabin Strain: Developing Weakness or Paralysis of Poliomyelitis†	Monkeys Which Received Sabin Strain: Developing Cord Lesions of Poliomyelitis
Intracerebral..	Undiluted	3/11‡	6/11	0/12	1/12
	10^{-1}	1/7	4/7	1/7	1/7
	10^{-2}	4/8	8/8	1/7	1/7
Intraspinal....	Undiluted	8/9	9/9	8/10	10/10
	10^{-1}	3/6	6/6	4/5	4/5
	10^{-2}	5/5	5/5	5/6	6/6
	10^{-3}	4/4	4/4	2/4	3/4
	10^{-4}	5/5	5/5	0/5	3/5
	10^{-5}	0/6	0/6		
	10^{-6}	0/5	0/5		

* Of 46 control monkeys inoculated intracerebrally and 28 inoculated intraspinally, none developed disease or lesions.
† Progressive weakness or paralysis beyond second day after inoculation.
‡ Numerator = number of monkeys positive; denominator = number of monkeys inoculated.

TABLE 2.—*Comparative Titrations for Neurovirulence of Type 2 Candidates for Orally Given Poliovirus Vaccine*

Route of Inoculation	Concentration of Tissue-Culture Fluid	Monkeys Which Received Lederle-Cox Strain: Developing Weakness or Paralysis of Poliomyelitis*	Monkeys Which Received Lederle-Cox Strain: Developing Cord Lesions of Poliomyelitis	Monkeys Which Received Sabin Strain: Developing Weakness or Paralysis of Poliomyelitis*	Monkeys Which Received Sabin Strain: Developing Cord Lesions of Poliomyelitis
Intracerebral..	Undiluted	5/10†	10/10	0/10	0/10
	10^{-1}	3/6	6/6	0/6	0/6
	10^{-2}	3/6	5/6	0/6	0/6
Intraspinal....	Undiluted	10/10	10/10	5/8	8/8
	10^{-1}	6/6	6/6	4/5	5/5
	10^{-2}	6/6	6/6	0/5	4/5
	10^{-3}	3/3	3/3		
	10^{-4}	2/4	3/4		
	10^{-5}	0/4	0/4		

* Progressive weakness or paralysis beyond second day after inoculation.
† Numerator = number of monkeys positive; denominator = number of monkeys inoculated.

TABLE 3.—*Comparative Titrations for Neurovirulence of Type 3 Candidates for Orally Given Poliovirus Vaccine*

Route of Inoculation	Concentration of Tissue-Culture Fluid	Monkeys Which Received Lederle-Cox Strain: Developing Weakness or Paralysis of Poliomyelitis*	Monkeys Which Received Lederle-Cox Strain: Developing Cord Lesions of Poliomyelitis	Monkeys Which Received Sabin Strain: Developing Weakness or Paralysis of Poliomyelitis*	Monkeys Which Received Sabin Strain: Developing Cord Lesions of Poliomyelitis
Intracerebral..	Undiluted	3/10†	3/10	0/10	0/10
	10^{-1}	2/6	2/6	0/6	0/6
	10^{-2}	0/6	0/6	0/6	0/6
Intraspinal....	Undiluted	8/10	10/10	9/10	10/10
	10^{-1}	6/6	6/6	3/6	6/6
	10^{-2}	6/6	6/6	3/6	6/6
	10^{-3}	4/4	3/4	0/4	2/4
	10^{-4}	1/4	2/4	0/4	0/4

* Progressive weakness or paralysis beyond second day after inoculation.
† Numerator = number of monkeys positive; denominator = number of monkeys inoculated.

in both the cervical and the lumbar areas, as shown by the high scores of 457 and 649, while Sabin's strain yielded a score of only 24. After IS inoculation in the lumbar area, the Lederle material showed a high degree of activity (lumbar score, 1,597) and spread into the cervical area (score, 844), i. e., ratio of cervical to lumbar scores of 1/2, while Sabin's material showed a lesser but significant spread, with the ratio of cervical to lumbar scores being 123 to 837, or about 1/7. A low ratio, such as 1/7, of cervical to lumbar scores indicates little spread of the virus from the area of injection while a high ratio, such as 1/2, indicates extensive spread of neurovirulent virus to the cervical area.

For type 2, Lederle's strain titered over 300 MPD_{50} per milliliter by the IC route and 200,000 MPD_{50} by the IS route, while Sabin's strain was negative by the IC but had a titer of at least 2,500 MPD_{50} by the IS route (tables 2 and 4). After IS inoculation, Lederle's strain showed a high degree of activity and of spread (ratio of cervical to lumbar scores, 1,009 to 1,778, or about 1/2) in contrast to the relatively low degree of activity and spread of Sabin's strain (ratio of cervical to lumbar scores, 44 to 346, or about 1/8) (table 4).

For type 3, Lederle's strain contained only 1 MPD_{50} per milliliter by the IC route but had a titer of 10,000 MPD_{50} by the IS route (tables 3 and 4). After IS inoculation, the differences in lesion scores between type 3 strains were less marked than for the other strains, and the degree of spread was also similar, a high ratio of cervical to lumbar scores of about 1/2 being found for both strains: Lederle ratio, 584/1,259; Sabin ratio, 355/850 (table 4).

The marked discrepancies between many of our titrations and those reported by Sabin and by Cox were surprising. It was on the basis of their findings that the WHO Expert Committee on Poliomyelitis [1] in 1957 recommended that strains be used in field trials only if there was a "complete lack of paralytogenic activity on IC inoculation of maximal doses (in excess of 10^7 TCD_{50}) in rhesus or cynomolgus monkeys and only minimal residual neurotropism by spinal inoculation in monkeys—i. e., only rare development of localized, nonprogressive paralysis in monkeys receiving doses of 10^6 TCD_{50} or more." Our results with both Sabin's and Lederle's strains have since been confirmed by a second impartial laboratory, the Division of Biologics Standards, National Institutes of Health.[2]

In criticizing our results, Sabin [3] implied that we produced so much nonspecific damage in the monkeys that the inoculation procedure and the retention of the inoculum in the cord might have been responsible for the paralytic manifestations. A series of control tests with normal tissue-culture fluids, with an enteric cytopathogenic human orphan (ECHO) virus, or with the vaccine strains diluted beyond their paralytogenic end-point, failed to produce disease or histological responses that in any way could be confused with those of poliomyelitis.

Our results indicate that children have been fed poliovirus strains possessing greater neurotropic activity than had been suspected, the degree of which is shown in table 5. (The same may be said for children fed Koprowski's strains, in view of the high degree of neurotropic activity found in these strains by Sabin [3] and by the Division of Biologics Standards.[2]) We have considered 0.01 ml. of infectious tissue-culture fluid, containing 10^5 TCD_{50}, as the dose generally used for human feeding with Sabin's strains, and 10^5 to 10^6 TCD_{50} as the dose with Lederle's strains. Thus one human dose of virus, the amount used to produce infection in the vaccinated child, contains from 100 to 30,000 poliomyelitis doses for the monkey inoculated by the sensitive intraspinal route.

TABLE 4.—*Comparative Titers of Candidate Strains of Live Poliovirus Vaccine*

Live Poliovirus Vaccine		50% Doses per Ml.					Poliomyelitis Lesion Scores*			
		Monkey Kidney Tissue Culture	Intracerebral Neurovirulence		Intraspinal Neurovirulence		Intracerebral Inoculation		Intraspinal Inoculation	
Type	Strain		Clinical Disease†	Poliomyelitis Lesions	Clinical Disease	Poliomyelitis Lesions	Cervical	Lumbar	Cervical	Lumbar
1	Lederle	$10^{7.3}$	$10^{2.0}$‡	$>10^{2.3}$	$10^{2.5}$	$10^{5.5}$	457	649	844	1,597
	Sabin	$10^{7.3}$	$<10^{0}$	$<10^{0}$	$10^{4.0}$	$10^{5.0}$	0	24	123	837
2	Lederle	$10^{8.9}$	$10^{2.0}$‡	$>10^{2.3}$	$10^{6.0}$	$10^{5.3}$	487	704	1,009	1,778
	Sabin	$10^{7.2}$	Neg.	Neg.	$10^{2.4}$	$>10^{2.4}$	0	0	44	346
3	Lederle	$10^{7.2}$	10^{0}	10^{0}	$10^{4.7}$	$10^{5.0}$	179	232	584	1,259
	Sabin	$10^{7.5}$	Neg.	Neg.	$10^{3.0}$	$10^{4.0}$	0	0	355	850

* Undiluted through 10^{-2} used for calculation of poliomyelitis lesion scores for monkeys inoculated intracerebrally, and undiluted through 10^{-4} for those inoculated intraspinally.
† Paralysis or weakness due to multiplication of poliovirus.
‡ Approximate figures.

Use of Tissue Culture Markers for Determining Genetic Changes in Attenuated Poliovirus.—Within the past two years, at least three markers of poliovirus have been described which can be followed by tissue culture methods and which tend to discriminate between neurovirulent and attenuated strains. Strains possessing the *d*+ marker grow more rapidly than *d*– strains at low bicarbonate concentration under agar [4]; strains possessing the *MS*+ marker grow more rapidly on the monkey stable kidney-cell line than *MS*– strains [5]; strains possessing the *T*+ marker grow readily at 40 C in

contrast to the *T*– strains.[6] Virulent, wild strains possess *d*+, *MS*+, and *T*+ markers and thus differ from most attenuated strains.

In the course of a study of a number of families in Mexico City who had been fed Sabin's attenuated strains in the spring of 1958, Ramos-Alvarez kindly made available to us serial specimens of rectal swabs from 81 vaccinated children and their family contacts. The details of the study and of the

TABLE 5.—*Amount of TCD_{50}, MPD_{50} (IC), and MPD_{50} (IS) in One Human Dose of Live Poliovirus Vaccine**

Vaccine Strain		TCD_{50}	MPD_{50}(IC)	MPD_{50}(IS)
Lederle	1	$10^{5.5}$-10^{6}	$10^{6.5}$-$10^{7.5}$	$10^{6.5}$-$10^{8.5}$
	2	10^{5}-10^{6}	$10^{6.5}$-$10^{7.5}$	$10^{6.5}$-$10^{8.5}$
	3	10^{5}-10^{6}	0	$10^{6.5}$-$10^{8.0}$
Sabin	1	$10^{5.5}$	0	$10^{6.0}$
	2	$10^{6.5}$	0	$>10^{7.4}$
	3	$10^{5.5}$	0	$10^{7.0}$

* MPD_{50} indicates dose producing specific poliomyelitis lesions in 50% of inoculated monkeys; IC = intracerebral and IS = intraspinal route of inoculation.

methodology will be reported separately. Here we wish to point out the usefulness of the method in being able to select, for the expensive monkey-neurovirulence tests, strains which have altered after multiplying in the human alimentary tract. In table 6 the results on 36 strains recovered from vaccinated children show that in 15 there was no detectable alteration in the virus, in 16 others the recovered virus changed in the *d* but not in the *T* marker, and in 5 others changes occurred in both markers. Thus, in 14% of the children infected with *d*–*T*– strains, the excreted viruses had changed in at least two properties. When a strain reverted from *d*– to *d*+, it was not always associated with a *T*– to *T*+ reversion. However, every instance of *T*– → *T*+ reversion was linked with a *d*– → *d*+ reversion.

Correlation Between Genetic Instability and Increase in Neurovirulence.—Strains recovered from the Mexican children fed Sabin's vaccine strains were selected for testing in monkeys. The strains had all been isolated in monkey-kidney cultures maintained in M-E medium at pH 7.4. (The M-E medium used contained 0.5% lactalbumin hydrolysate and 1% monkey serum, in Earle's balanced salt solution.) However, to insure that we were not selectively enhancing the proportion of monkey paralytogenic strains by passage of the human virus in tissue culture, a number of rectal swabs obtained from the vaccinated children were inoculated directly into monkeys by the intraspinal route. The dose of virus in such material which could be inoculated was very small indeed, varying from only 10 to 60 TCD_{50}.

A summary of the monkey tests on strains of the 3 types is shown in table 7. It is apparent that excreted strains which retain the *d*–*T*– markers of the vaccine virus are not significantly more virulent for monkeys than the vaccines themselves, about 10,000 TCD_{50} being required to paralyze 50% of the monkeys inoculated intraspinally, and no illness being produced either by undiluted tissue-culture fluid inoculated intracerebrally or by the rectal swabs inoculated intraspinally. The *d*+*T*– strains show increased activity, both intraspinally and intracerebrally, when compared to the *d*–*T*– vaccine virus. Thus, only 10 TCD_{50} of the cultured virus were found to contain one monkey-paralyzing $dose_{50}$ (intraspinal), and some of the strains were also active after intracerebral inoculation. Furthermore, 10 to 60 TCD_{50} of virus in the rectal swabs themselves produced paralysis in a significant number of test monkeys inoculated intraspinally.

The strains which changed in both markers to *d*+*T*+, showed even greater neurovirulence. One strain (recovered from a 2-month-old vaccinated child) which had reverted to the *d*+*T*+ state, was selected for inoculation not only into monkeys but also into a chimpanzee, as members of this species are known to be much less sensitive to attenuated poliovirus than monkeys. Only 10 TCD_{50} of passage virus, or the same small dose as present in the rectal swab, produced paralysis when inoculated intraspinally in monkeys; in addition, the undiluted passage virus proved to be paralytogenic in monkeys inoculated intracerebrally and also in the chimpanzee inoculated intraspinally.

Cytopathogenic virus was recovered from the spinal cords of almost all monkeys sacrificed soon after the onset of paralysis, indicating that no selection of strictly neurotropic virus had taken place in the central nervous system of the monkeys.

Field Trial

Interfering Effect of Enteroviruses Circulating in a Population on Immunizing Capacity of Attenuated Poliovirus.—In the course of the 1958 family study in Mexico City already referred to above, 596 postvaccination stool specimens were tested. Of these, a total of 237 specimens exhibited a cyto-

TABLE 6.—*Markers of Polioviruses Excreted by Vaccinated Children Orally Infected with Sabin's Attenuated Strains*

Markers of Vaccine Virus Used to Initiate Infection	Poliovirus Types	Viruses Excreted by Vaccinated Children: Total Tested	d–T–	d+T–	d+T+
d–T–	1	16	12	4	0
d–T–	2	8	2	6	0
d–T–	3	12	1	6	5
Total		36	15	16	5

pathogenic agent in monkey-kidney cultures. Only 37% were homotypic polioviruses, i. e., polioviruses of the same type as in the vaccine fed, while 57% proved to be enteroviruses other than poliovirus. Table 8 illustrates the interfering effect of the latter on infection with the vaccine viruses and on poliomyelitis antibody formation. Of 28 children who were free of enteroviruses before feeding, 22 developed antibodies against the vaccine virus. Poliovirus was isolated from 18 out of these 22 children. On the other hand, 33 of 47 children excreting other

enteroviruses failed to produce antibodies to the vaccine viruses, and only 3 out of these 33 excreted poliovirus. The interference of the enteroviruses, although marked, was not complete, for the remaining 14 of the 47 children did produce antibodies, and of these 14, 10 excreted homotypic polioviruses in spite of the competing infections with other enteroviruses. The detailed analysis of this study will be reported together with Dr. Manuel Ramos-Alvarez.

Measurement of Degree of Safety of a Vaccine in the Field.—It seems obvious that only susceptible persons should be considered in evaluating the results of a field trial. In the study in Mexico City,[7] the number of children with poliomyelitis antibodies prior to the feeding of vaccine was already 33% in those one year of age, 54% in the 2-year-olds, and 85% in those 3 to 5 years old. Feeding in such a population is significant only if the children under 3 years of age are considered, and even in this population the number of those susceptible is far less than the total number fed. Feeding virus to children having contacts who are chiefly immune by natural infections tells very little about the safety of a vaccine for a community, for the opportunities of spread in immune populations are severely limited. Thus, if 100,000 children 3 to 5 years of age are fed virus, in a population whose natural immunity has reached 85% by this age, the actual "test group" of vaccinees is reduced to only 15,000, and the number of their susceptible contacts is likewise only a small fraction of the population.

Another factor in the evaluation of such studies must be the consideration not only of the number of children fed but also of the number of cases of poliomyelitis expected if the same population had been exposed to virulent poliovirus. In this way an answer can be sought as to how much safer is infection with the vaccine than infection with virulent epidemic poliovirus. At least two kinds of data are available to arrive at such figures.

In the unfortunate experience during 1955, in which live virulent virus escaped inactivation in certain lots of Salk vaccine, a number of paralytic cases occurred among vaccinated children. Two studies, one by the neutralization test [8] and one by the complement-fixation test,[9] indicated that high antibody titers were present in 31 to 40% of children six to eight weeks after receiving a single intramuscular dose of the vaccine containing live virus, in contrast to 1 to 8% in control, nonvaccinated children in the same area, or in children receiving a single dose of properly inactivated Salk vaccine. As 20 type 1 (virulent Mahoney strain) cases of poliomyelitis occurred among 32,000 children vaccinated with the inadequately inactivated lots, the serologic data indicate that the 20 cases occurred among some 10,000 "infected" children, or 1 case per 500 infected. However, the argument might be raised that these children were infected by an unnatural route.

Another approach to this problem has been made by studying the acquisition of poliomyelitis antibodies during a severe type 1 epidemic, allowing us to determine subclinical infection rates.[10] The analysis showed that one paralytic case occurred for approximately 100 children infected with the epidemic virus.

Thus, before any claims of safety can be made with regard to an orally given vaccine, large numbers of children must be used. A study involving only 100 children, even if all are susceptible, would be expected to yield no more than a single case if the virus were of the wild, virulent type. For this reason, small studies involving a few hundred susceptible children, as recently carried out in Minnesota,[11] yield very little evidence of safety; the expected cases, even with virulent virus, would be too few in number to indicate how much safer the vaccine virus is than virulent virus.

TABLE 7.—*Correlation of* d *and* T *Characters of Poliovirus Strains with Monkey Neurovirulence*

Strains	No. of Strains Tested	Characters* d	Characters* T	No. of Monkeys with Clinical Poliomyelitis/No. Tested; Log TCD_{50} Inoculated; Intraspinally 4.5-4.2	Intraspinally 3.5-3.0	Intraspinally 2.5-2.0	Intraspinally 1.0	Intracerebrally 7.5-6.2	Rectal Swab Intraspinally 1.5-1.0
Vaccines fed	3	−	−	8/18	2/8	0/9		0/32	
Viruses excreted	6	−	−		9/11	0/9		0/2	0/6
	1	±	−			2/2			2/2
	8	+	−		2/2	16/16	4/13	2/6	3/9
	2	+	+			4/4	3/4	5/5	2/2†

* d and T characters were each established by repeat tests.

† Of these two strains, material from only one rectal swab was available in sufficient amounts for testing in monkeys. This material possessed the T+ marker. All other rectal swabs were T−. No d character tests were performed with rectal swabs.

Comment

The 1957 report of the WHO Expert Committee on Poliomyelitis [1] lists one of the "criteria which should be fulfilled in the design of carefully controlled field trials," as follows: "It is suggested that the properties of these attenuated strains which can be tested in the laboratory, be measured in a number of different laboratories so that there can be more than one opinion as to their pathogenicity or the lack of it."

Data now accumulating from this and other laboratories [12] indicate serious disagreement with the degree of attenuation claimed for the viruses being fed and also for the degree of reversion being found in the virus which multiplies in, and is excreted by, some of the vaccinated children. We do not imply that we have proved that such virus

strains are dangerous either for the vaccinated child or for the community, but we wish to emphasize that the risks appear to be greater than had been suspected and that much more knowledge must be obtained concerning how the viruses may be altered in persons living under different macroclimatic and microclimatic conditions, before the available attenuated strains can be said to meet the criteria of a safe and effective vaccine for the control of poliomyelitis.

The data on monkey neurovirulence presented in our paper, and those of the Division of Biologics Standards,[2] were obtained with a slight refinement in testing methods. They reveal that the orally given vaccines currently in field trial are much more neurovirulent than had been found by the proponents of the vaccine. Indeed, Sabin himself has reported [3] that the Lederle and Koprowski strains in his hands are more neurovirulent than has been reported. In view of these findings, the question of safety has now changed from the one originally posed. Originally, investigators in this field had

TABLE 8.—*Influence of Infection with Other Enteroviruses Before Attenuated Poliovirus Vaccine Feeding on Homotypic Antibody Production Against Vaccine Virus*

	No. of Children Who Did Not Excrete Other Viruses Before Vaccine Feeding			No. of Children Who Excreted Other Viruses Before Vaccine Feeding		
Antibody Status	Total	Excreted Polio-virus	Did Not Excrete Polio-virus	Total	Excreted Polio-virus	Did Not Excrete Polio-virus
Homotypic antibody rise after feeding	22	18	4	14	10	4
No homotypic antibodies before or after feeding	6	0	6	33	3	30
Total	28	18	10	47	13	34

asked: "Are the attenuated viruses, which are almost free of monkey-neurotropic activity, safe immunizing agents for man?" The question must now be phrased: "How much monkey-neurovirulent activity may a strain safely possess if it is to be used for infecting and immunizing children?" The answers seem to be coming in from the increasingly large-scale tests being carried out on children by many investigators. In the course of these trials, an answer might also be obtained on another uncontrollable factor in the epidemiology of poliomyelitis: Do different microclimates and macroclimates influence virus-host relationships, so that what is safe for the host under certain circumstances may become dangerous if those circumstances change? Virulent and attenuated poliomyelitis strains may circulate year in and year out in communities, conferring a high degree of immunity, with little associated disease, and suddenly paralytic cases may begin to appear in the population. The reasons for the initiation of epidemics have not yet been adequately explained.

At this time, it is the question of genetic stability of the vaccine virus which is of primary importance [12] rather than questions of dosage, order of feeding of strains, etc., to which many investigators are giving their attention. Obviously, if one selected random samples from vaccinated children for testing for monkey neurovirulence, one might choose strains which had not altered in the human alimentary tract—particularly if such strains were the predominant ones being excreted. In table 6 it can be seen that only 5 of 36 strains showed reversion in two characters, and it was these markedly altered viruses which showed the greatest reversion in monkey neurovirulence. Not only did they become paralytogenic for monkeys inoculated in large doses by the intracerebral route but as little as 10 tissue culture doses of the reverted viruses were sufficient to produce paralysis in monkeys inoculated by the intraspinal route. It is only these altered viruses in the progeny of the vaccine virus which are apt to be dangerous as they are passed about, under no control, in the community. Whether or not viruses which alter soon after they begin to multiply in man may ever enter the vaccinee's brain and spinal cord is not known. Certainly, judging from the large number of persons who have been given these vaccines, the danger does not appear great. However, until more is known about the factors which turn a harmless carrier into a paralytic patient, this is a feature which cannot be controlled.

At the PAHO-WHO Washington Conference of June, 1959, the comment was made again and again, by proponents of live virus vaccination, that the significance of monkey neurovirulence is not understood. Neurotropic activity for monkeys may not indicate a similar activity for children. However, the criteria for the selection of strains for feeding were based on reduction of neurovirulence for monkeys, and it seems obvious—to us at least—that this character should be established as a stable one before large-scale feeding of live virus is continued. In this regard it is noteworthy that, among Sabin's strains, it was the type 3 which showed the greatest spread within the spinal cord (table 4), and it was this same strain which underwent the greatest increase in monkey neurovirulence after human passage (tables 6 and 7).

The problem of viral interference was mentioned by several investigators (Gelfand, Sabin, Paul, and Gear) at the Washington conference. The enteric tract of a child may be temporarily committed to the production of a nonpoliomyelitis enterovirus, blocking the establishment of infection and immunity by the vaccine virus in as many as 50% of poliomyelitis-susceptible children (table 8). A vaccine with such a low rate of effectiveness, even if safe, would leave much to be desired. Whether increasing the dosage will overcome this viral interference without decreasing the safety margin of the vaccine, as suggested by Cox, remains to be determined by future investigations.

Other problems, on which our experimental data do not bear but which have yet to be met before

the attenuated strains can be said to meet the criteria required of human vaccines, are discussed below:

First, the reproducibility of the properties of the vaccine from one lot to the next must be established. Only a single large lot of Sabin's strains has been produced in the United States, although recent work in the U. S. S. R. is now going forward with further "production" lots. How will each lot be tested, not only for residual monkey neurovirulence but also for genetic stability and spread in man? Will separate field trials have to be run with each lot? Can the data obtained from a field trial in one part of the world be used to indicate the safety and potency response in another part of the world, where the children have different bacterial and viral flora in their enteric tracts?

Second, the attenuated poliovirus strains are being prepared in monkey-kidney cultures, which often contain adventitious viral and other agents.[13] One of these, B virus, is known to produce fatal infections in man.[14] It is now eliminated from consideration by testing small portions of a large batch of vaccine, in rabbits. Are enough data at hand to say that a human being is no more susceptible than the rabbit or that testing a small volume of vaccine is enough to insure the absence of this dangerous virus from the entire lot? One should also bear in mind that many other simian viruses exist and that they have been little studied. Their detection may be handicapped by the fact that sensitive and reproducible tests have not yet been developed for many of them. A controversy now exists between Sabin[3] and Koprowski,[15] in which the former claims that a wild simian virus was present in Koprowski strains fed to over 50,000 persons in Africa, Poland, and Sweden.

Summary and Conclusions

Tests in monkeys of the live poliovirus vaccines currently being used in field trials have shown them to be more neurovirulent than was found in the laboratories of the proponents of the vaccines. The range of neurovirulence varied from the least virulent (Sabin's type 2)—which reacted negatively after intracerebral injection but contained at least 2,500 monkey poliomyelitis doses per milliliter after intraspinal injection—to the most virulent (Lederle's types 1 and 2) which contained at least 300 monkey doses per milliliter by intracerebral injection and 300,000 monkey doses per milliliter by intraspinal inoculation. The higher titers found by intraspinal injection seem to hinge on the use of a fine needle and the retention of the virus inoculum within the spinal cord.

The degree of genetic stability of the attenuated poliovirus as it undergoes multiplication cycles in vaccinated children and their contacts is of the utmost importance.[12] The use of tissue-culture markers for monitoring the stability of attenuated strains in the field is illustrated in a study of Sabin's strains fed to children in Mexico City. The excreted viruses which showed the greatest alteration in the tissue-culture *d* and *T* markers also showed the greatest increase in monkey neurovirulence (active after intracerebral injection, and only a few virus particles sufficing to paralyze monkeys after intraspinal injection). One altered strain was tested in a chimpanzee and found to be paralytogenic when inoculated intraspinally. That the increased monkey neurovirulence was not a laboratory artifact, brought on by cultivation of the virus under conditions favoring the growth of virulent particles, is shown by the finding that the few virus particles present in rectal swabs (10 to 60 tissue culture doses) were sufficient to paralyze monkeys inoculated intraspinally.

In the course of the Mexican study, it was found that many serologically susceptible children (i. e., free of poliomyelitis antibody) were resistant to infection by the vaccine. As such children were found to be already excreting a nonpoliomyelitis enterovirus at the time the live poliovirus vaccine was fed, the resistance has been attributed to the current infection with the nonpoliomyelitis enterovirus blocking the implantation of the vaccine virus. Interference of this sort might well limit the effectiveness of an orally given vaccine in areas where enterovirus infections are common.

The question of safety of the live poliovirus vaccine resolves itself on the frequency of disease in vaccinated children and their contacts, as compared with that anticipated from natural infection with wild polioviruses. In measuring the safety and effectiveness of live poliovirus vaccine, field investigators should consider not only the number of children fed but also the number already naturally immune and the number of poliomyelitis cases to be expected if the same population were exposed to virulent virus.

If caution was called for in 1954 and 1955 when the Salk vaccine was introduced into large-scale field use, then caution should also be the watchword now.

This study was aided by a grant from the National Foundation. The comparative study of the candidate vaccine strains in monkeys was also supported by a grant from the Lederle Laboratories, Pearl River, N. Y.

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"CONSTITUTIONAL" ALLERGIC REACTIONS AND THEIR PREVENTION

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As the name implies, in a "constitutional," "systemic," or "generalized" reaction (excluding delayed reactions of the serum sickness type) the allergic process is not confined to a single shock organ such as the bronchial tree or to the nose and sinuses. It involves practically every organ of the body, notably the skin and the mucous membranes of the respiratory tract. There is, however, a tendency for the allergic reaction to concentrate in a preexisting shock organ.[1] For instance, when a patient with dermatitis develops a constitutional reaction dermal manifestations predominate and in one afflicted with asthma, asthmatic symptoms. An allergic reaction initiated by severe uterine or gastrointestinal spasms after an overdose of pollen extract is relatively rare.

Manifestations

The classic type of reaction [1] begins with tingling and itching in the palate, palms, and genitalia, with sneezing, conjunctival edema, and a dry nonproductive cough. Generalized urticaria and allergic respiratory symptoms, especially bronchial asthma, follow in short order. In severe shock, especially

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The major occasions for constitutional allergic reactions are intradermal tests with allergens, treatments with antigens, sclerosing injections for varicose veins, local anesthetics, injections of radiopaque mediums for roentgenographic diagnosis, injections of antibiotics and hormones, inhalation of airborne substances, and ingestion of foods or drugs to which the patient is sensitive. Treatment of reactions must be prompt. Epinephrine and a tourniquet are the first standbys. Intradermal tests should be done only on arms and legs where a tourniquet can be applied and not on the back. Penicillin should never be given without a preliminary intradermal test and should not be injected into the hips or trunk where a tourniquet cannot be applied. The danger is lessened by proper timing of injections and by preliminary injection of a small test dose of a drug before the full intended dose is given.

after an intravenous injection, death may occur so precipitously that no symptoms other than collapse are noticeable. This is also true in persons whose sensitivity has been acquired, as, for instance, in some of the fatalities reported from penicillin. Here autopsies reveal petechial hemorrhages and edematous changes in the lung tissue and other vital organs instead of urticaria, bronchospasm, emphysema, and accumulation of mucus in the bronchial tree.[2] It seems that these patients, like animals in anaphylactic shock, do not yet have the ability to react to the sudden influx of the antigen into the system as an asthmatic patient does during a constitutional reaction.

In contrast to a delayed reaction of the serum sickness type the immediate constitutional reactions rarely produce any lasting effects. Indeed, existing allergic symptoms are often controlled temporarily by the reaction. Occasionally, however, a pneumonitis or a sinus infection may ensue, especially when the symptoms have not been promptly controlled.

Causes.—Allergic reactions are caused by injected, ingested, and inhaled antigens. The major occasions for reactions are intradermal skin testing and antigenic treatments; sclerosing injections for varicose veins; injections of local anesthetics or opaque mediums for x-ray studies; antibiotics, vitamins, and gland products, including insulin and ACTH; inhalation of airborne substances; and ingestion of foods and drugs to which the patient is very sensitive.

Of particular concern to general practitioners are reactions from injections of penicillin and ingestion of aspirin tablets. Allergists are most frequently confronted with reactions from therapeutic injections and from intradermal skin tests. Regardless of whether the agent is an organic or inorganic chemical, protein or nonprotein, the symptoms produced are identical.[3] It is true that very small doses may elicit a reaction, but the larger the dose the greater the risk.

Differential Diagnosis.—Various kinds of reactions may follow a hypodermic injection such as febrile reactions from contaminated glass and rubber utensils, a flare-up of a dormant focus of infection, or a pulmonary thrombosis. Such reactions must be differentiated from allergic shock. In our daily practice, however, mainly two conditions give rise to confusion, namely, syncope and the toxic effect from an ingested or injected drug. Syncope can be recognized promptly by bradycardia and pallor of the face as distinguished from tachycardia and flushing of the skin in the allergic reaction.

The vasodilating effect of an intravenous injection of aminophylline, or the toxic action of a local anesthetic in a patient intolerant to the drug, may be confused with an allergic reaction. I have presented [4] clinical and autopsy data on two fatalities occurring after administration of procaine (Novocain) hydrochloride; one appeared to be due to intoxication from an accidental intravenous injection, in a patient debilitated by chronic illness, and the other was probably the result of allergic shock.

Modes of Reactions.—Experience with pollen injections has taught us to distinguish three modes of allergic reaction (see table), namely, from an overdose, from an accidental intravenous injection, and from backseepage.[5]

A reaction from an overdose is initiated by a local edema at the site of injection. This can be seen expanding along the lymph channels before generalized urticaria and respiratory symptoms ensue. In an overdose reaction there is a lapse of a few minutes to an hour or more before generalized symptoms arise. The shorter this time interval the more severe the reaction.

This is in contrast to the immediate onset and immediate climax of a reaction to an intravenous injection, in which there is no local edema. This type of reaction invariably constitutes an emergency.

A backseepage reaction is due to injection of antigen next to and seepage into an accidentally punctured vein. It develops within one to several minutes. A local edema forms rapidly with extensive wheal formation. Blood may appear at the site of the injection, and often a bloody suffusion is present. The reaction is characterized by shock and collapse.

Allergic Reactions from Pollen Injections

	Type		
	Intravenous	Backseepage	Overdose
Incidence[5]	1:9,887	1:1,564	1:308
Onset after injection	10 to 20 sec.	1 to 5 min.	Depends on severity
Local reaction	No	Yes	Yes
Blood at site of injection	Often	Usually	Rare
Use of tourniquet	Ineffective	Effective	Effective

Treatment.—In treating an allergic reaction the speed with which medication is administered determines the outcome. The lapse of even a minute can be decisive. Therefore, various therapeutic agents should be available for instant use.

Epinephrine and a tourniquet are our first stand-bys. In intravenous and backseepage reactions doses as large as 1.0 cc. should be given. They may have to be followed up with subsequent doses of 0.5 cc. within a few minutes or at longer intervals to be determined by the patient's response. In the more slowly developing overdose reaction a dose of 0.1 to 0.2 cc. is necessary. It can be repeated several times. A tourniquet [6] applied above the site of the injection in order to slow down absorption of the injected antigen has proved most valuable in the control of both overdose and backseepage reactions. It is useless when the injection has been given into a vein.

Then, if allergic edema predominates, an antihistaminic such as diphenhydramine (Benadryl) hydrochloride, 2 to 5 cc. (20 to 50 mg.), should be

administered intravenously. If asthma is the predominant symptom, aminophylline, (0.5 Gm.), should be given intravenously. In severe shock the needle should be kept in the vein, in order to be prepared to give epinephrine intravenously in doses of 0.1 to 0.3 cc. This should be injected slowly, mixed with blood drawn into the needle, in order to minimize the danger of cerebrovascular and cardiac damage from the drug. On two occasions intravenous administration of epinephrine has appeared to be of great benefit after other procedures have failed.

Intermittent positive pressure or the Pulmotor of the fire department have also been of considerable assistance. Respiration can be maintained by forcing oxygen and carbon dioxide into the collapsed and spastic bronchi.

Intravenous administration of steroid preparations is of no avail in the control of an immediate reaction, but therapy with steroids can be given after the other drugs and will undoubtedly enhance the speed of recovery. The value of glucose and of calcium preparations for intravenous administration has not been conclusively demonstrated.

In reactions of minor severity too extensive treatment, especially with epinephrine in oil and antihistaminics, tends to produce more discomfort to the patient than the reaction itself.

Prevention of Constitutional Reactions

The incidence of reactions is proportionate to the caution employed by the physician with respect to hypodermic injections, his conservatism in gauging the doses of antigenic treatment, and the competence of his personnel. Needless to say, epinephrine, a tourniquet, and the other therapeutic agents must always be available for prompt action.

Intradermal Skin Testing.—It is fallacious to assume that preliminary scratch tests are a safeguard against constitutional reactions, which occur in spite of negative results of scratch tests, especially if the testing material employed for the scratch tests has lost its potency because it has been on hand too long. In infants and young children, who are notably more susceptible to reactions than adults, intradermal skin testing should be done sparingly. Instead, the passive transfer method should be employed.

When the patient's history discloses that ingestion or inhalation of a certain antigen has in the past given rise to allergic shock, a C, for "caution," entered on the record for this particular antigen signifies that it must automatically be omitted from intradermal testing. If it becomes necessary to treat the patient for this substance his degree of sensitivity must first be titrated with adequately diluted extracts.

Intradermal tests for antigens to which reactions are known to occur more readily, such as nuts, fish, and beans, should be done last. If the initial tests for other antigens have produced strong positive reactions, and thus indicate a marked sensitivity of the patient, subsequent tests should be omitted altogether or done by the scratch method. Fungi and pollens are well suited for preliminary evaluation of the patient's sensitivity. For use in testing patients with excessive sensitivity, the extracts customarily used should be diluted 1:10 or 1:100.

Intradermal skin tests should be performed only on arms and legs where a tourniquet can be applied and not on the back. One should attempt to avoid superficial veins. The tests should be done in an area where the patient can be constantly observed by the physician or his personnel.

Antigenic Treatments.—Overdose reactions can be prevented by using conspicuous labels to distinguish between various concentrations of extracts; by using syringes of different colors for extracts of high and low concentration; by thoroughly cleansing the syringes before they are sterilized; by conservatively gauging the patient's sensitivity; and by adequately reducing doses when changing to fresh, more potent extracts in cases where a previous overdose reaction has occurred. The patient should be kept in the office for at least 10 minutes after the injection so that the injected site can be inspected for excessive wheal formation. An overdose reaction can be predicted from the appearance of the injected area.

In order to prevent reactions from venipuncture an area between visible veins should be selected for the injection. Before injecting the extract the plunger should be withdrawn for evidence of blood. The site injected should be inspected immediately after the injection for escaping blood, which is sometimes—in venous bleeding—a sign of an imminent reaction. Cotton should be applied with pressure on the area where blood is escaping in order to counter backseepage. Self-administration of antigenic extracts should be prohibited. In spite of all these precautions, however, there is no absolute safeguard against accidental venipuncture.

Use of antihistaminics or epinephrine in conjunction with antigenic treatment has been suggested. However, these agents reduce the local swelling and may be inconsistent in their prevention of constitutional reactions. They may thus interfere with the orderly progress of desensitization, although they do not modify the protective effect of the antigen.

Penicillin Injections.—Because of the ever-increasing number of fatalities from penicillin injection, both reported and unreported, this problem deserves special attention. In allergic patients treatment with penicillin should be avoided whenever other antibiotics can be used instead. If the patient's history reveals a previous reaction to penicillin, of either the serum sickness or the immediate generalized type, it should be employed only in an emergency.

In this case an intradermal skin test with an aqueous solution diluted about 1:100 should precede the injection; if the result is negative this should be followed by the intradermal injection of 0.05 cc. of the penicillin compound, the total dose to be administered 15 minutes later. Previous doses of epinephrine or ephedrine-like drugs, or of antihistaminics, interfere with a positive reaction. Therefore, a negative test result within four to six hours of the use of these drugs is unreliable. Under no circumstances should penicillin be used if the result of a skin test is positive; i. e., if it exhibits a definite wheal formation. Even if the result is negative, the penicillin injection should be preceded by an injection of an antihistamine and/or epinephrine. This precaution is likely to reduce the severity of an anaphylactic reaction, but it will not prevent it.

In less urgent cases careful testing, by titration, of the patient's sensitivity and systematic short-interval hyposensitization with very weak dilutions should precede its administration. The principle of this treatment and its technique, originated by Freeman,[7] has been outlined elsewhere.[8] A dilution of an aqueous solution of penicillin low enough to induce only a medium-sized wheal is injected intradermally. The doses are then carefully increased every one to three hours in such a manner that only local reactions of a moderate degree result. The success of this treatment depends on (1) starting with a low enough dose to produce only a small local wheal at the site of the injection, and (2) discontinuing the injections for at least four hours at any time when the local edema appears to be excessive or when a generalized reaction threatens. Whereas I have had considerable experience with this method in diminishing sensitivity to other antigens, I have employed it in only two asthmatic patients in whom penicillin had previously induced generalized reactions. Positive intradermal reactions were obtained with an aqueous dilution of penicillin of 1:10,000 (3 units) and 1:1,000 (30 units) respectively. In one of the patients a dose of 300,000 units of aqueous penicillin could be administered after three days; in the other this dose could be given after five days.

Penicillinase is not likely to be of assistance in treating an immediate reaction from penicillin. Penicillin should not be injected into the hips or trunk where a tourniquet cannot be applied. Inspection of the patient's arm 10 minutes after an injection is a precaution that cannot be too strongly emphasized.

In my experience a time interval of 10 days to six weeks between one injection and another appears to be more conducive to the development of penicillin sensitivity than injections given daily or every second or third day. In other words, the history of injections having been given from 10 days to six weeks previously calls for greater caution. In experimental anaphylaxis the optimal interval between the sensitizing and shocking injection is between 10 and 20 days.

Inhaled and Ingested Antigens.—Constitutional reactions after eating a certain food, inhaling the dander of a certain animal, or excessive exposure to pollen necessitate that the patient carry with him a nebulizer containing epinephrine or a related compound or sublingual isoproterenol (Isuprel) hydrochloride tablets which act within three minutes; antihistaminics or, in the more severe cases, an outfit for injection of epinephrine should be available to him. In my experience even the most severe sensitivity to foods as well as inhalants can be controlled by proper hyposensitization procedures.

Drugs.—Among drugs the most common and most dangerous reactions follow the use of salicylates. It has been stated that patients with nasal polyps are particularly susceptible, perhaps because of their frequent intermittent use of this drug for relief of headaches. A similar situation prevails in asthmatic women with a habit of taking aspirin intermittently at four-week intervals during their menses. Such patients should be alerted to this sensitivity, as their strict avoidance will prevent future trouble. Other analgesics, e. g., acetanilid, or even a mild narcotic, such as codeine, can be substituted for control of pain.

The value of skin testing for drugs is doubtful; conjunctival tests are occasionally of assistance in diagnosing sensitivity to drugs. Tuft's use of the buccal test[9] for determination of drug sensitivity may have merit.

For prevention of allergic reactions from local anesthetics and from sclerosing injections of veins a preliminary small amount should be administered before giving the total dose; 0.05 cc. of a local anesthetic may be injected intradermally into the oral mucosa as a test. If such a small dose elicits a constitutional reaction, it will be less severe than one from a full dose. With orally administered antibiotics a preliminary small oral test dose is recommended prior to administration of the full dose. Patch tests and conjunctival tests may or may not be of value.

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THE INCREASING INCIDENCE OF CARCINOMA OF THE THYROID IN A SURGICAL PRACTICE

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A total of 117 persons with thyroid carcinoma were admitted to a hospital in a period of 15 years. The number from 1943 to 1953 was 34, and the mean annual morbidity for that period was calculated to be between 3 and 4. The mean annual morbidity for thyroid carcinoma in the next five years (1953 to 1957) was between 16 and 17, a marked increase over the previous period. One-fourth of this increased morbidity was accounted for by valid reasons such as the great number of patients seen at the hospital and examined for diseases of the thyroid. Since only a part of the apparent statistical increase in thyroid carcinoma could be accounted for, further investigation is desirable. The possibility that there has been an actual increase in the occurrence of carcinoma of the thyroid could not be ignored.

The value of surgery in the eradication and prophylaxis of thyroid cancer has been under continuous study at the Henry Ford Hospital during the past four years. Beyond these practical aspects, studies have been made of the morbidity and mortality implications of thyroid cancer and yearly statistics have been compiled so that results of current therapeutic principles might be critically inspected. In 1953, the paucity of patients with thyroid cancer in a large medical practice was evident in that 34 cases had been seen in the preceding 10 years, or between 3 and 4 a year. By contrast, 83 cases were seen in the five years from 1953 through 1957, or between 16 and 17 cases per year. Since our surgical approach emphasizes the removal of suspicious nodules rather than indiscriminate removal of all thyroid lesions, it was necessary that this striking increase in incidence be evaluated with considerable care. The volume of medical literature dealing with thyroid cancer led us to believe that such a study would be of general as well as local interest.

Throughout this study, patients with thyroid cancer have been divided into two groups. Group 1 comprises all patients with cancer in whom preoperative cancer suspicion ranged from "none at all" to "a high degree" but in whom a clinical diagnosis was not definite. Group 2 contains those patients in whom metastatic disease was revealed or patients with local findings which left no reasonable doubt as to the correct diagnosis. Comparison of these classifications for the two periods from 1943 to 1952 and from 1953 to 1957 reveals that in the first period, 19 group 1 cancers were found in 438 operations for nontoxic nodular goiter. Fifty-six cancers and 636 operations were parallel figures for the second period. There were 15 group 2 cancers in the first period and 27 in the second.

The factors that we have considered in an attempt to account for these striking figures are as follows: (1) an increase in the number of patients, (2) more thyroidectomies in proportion to the number of clinic visits, (3) the possibility that professional growth might have attracted more referrals, (4) better criteria for pathological diagnosis, (5) improved clinical selection of cases for operation, (6) greater awareness of the possibility of cancer in

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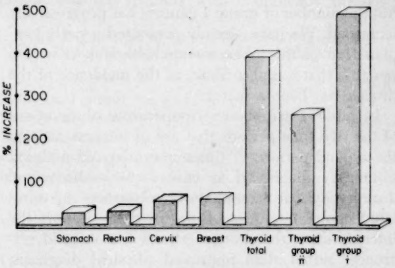
the general population, and (7) the possibility that there has been a real increase in the incidence of thyroid cancer.

Most institutions, medical and otherwise, normally manifest growth with age, and a simple increase in the number of cases of a disease might well be related to this growth. During this second period, 40% more patient visits per year were recorded than for the earlier period. As shown by the figure, four of the more common types of cancer increased in number during this period to a degree anticipated by institutional growth. Cancer of the breast, for example, increased from 45 to 67 cases per year, while cancer of the rectum increased from 35 to 45 cases per year; for both, an average gain of 40%. In sharp contrast is the increase for all thyroid cancer of 390%; group 1, 490%; group 2, 260%.

The growing reputation of an institution for the treatment of one disease or another may result in an increased number of patients referred by family physicians, or of self-referrals when the diagnosis has been established elsewhere. The majority of patients in the present study were self-referred without an established pathological diagnosis. Of the patients with group 1 cancers, three in each period of study were physician-referred, an increase for the second period since it was half as long. Of the patients with group 2 neoplasms, six in the first period and nine in the second were physician-referred or had a previous pathological diagnosis. This represents a greater, though not striking, increase than for the patients with group 1 cancers. These figures statistically are not significantly different but they do indicate that, at best, selective referrals cannot explain more than a small part of the observed increase.

The number of patients with thyroid cancer can be increased in any practice by the simple expedient of increasing the number of thyroidectomies. Judged by Mortensen's statistics from the Mayo Clinic,[1] careful pathological examination of palpably normal thyroid glands should yield two cancers per 100 thyroidectomies, and indiscriminate removal of all glands that are nodular by palpation should raise this number to about four. Our own figures bear this out,[2] and since from 1953 to 1957 the number of thyroidectomies increased from 44 per year to 125 per year, an average of 3 additional cancers each year was assured. With institutional growth accounting for 20% of the increase in the number of operations, these two factors together account for an increase of only about 40% of the increase in patients with group 1 cancers. The number of operations, of course, does not influence the increase in group 2, since these thyroidectomies were performed with a reasonably assured clinical diagnosis of thyroid cancer.

The pathological diagnosis of carcinoma of the thyroid has long been controversial, as witness the eras of "benign metastasizing struma" and "lateral aberrant thyroid." The past decade has seen great improvement in the pathological diagnosis of tumors in general, and outstanding progress has been made in regard to thyroid carcinoma. With this in mind, we have reviewed thyroid tissue from 175 surgically treated patients whose thyroid lesions were originally diagnosed as benign in the 1943 to 1952 era. The same number for the years 1953 to 1955 were re-studied microscopically by one of us (R.C.H.) who has made all the histological diagnoses in 1956 and 1957. Three previously undiagnosed cancers, one of which was occult, were recognized among the 175 cases in the earlier period, and five additional cancers were found in the later group. The number of additional cancers thus found is too small to furnish a basis for accurately estimating the total number of cancers, had all the thyroid cases been reviewed and all material from every case carefully reexamined. It is of interest, nevertheless, to use the results of this review, which represents 45% of the pertinent material, to project hypothetical figures for the corrected total incidence of thyroid cancer for each time period. On this assumption, the corrected total of group 1 cancers would be 26 for 1943 to 1952, and 65 for 1953 to 1957. This still represents a percentage increase of 400, as compared to the 490 derived from the uncorrected figures. Obviously, the improved criteria for pathological diagnoses offer only a partial explanation.



Increased diagnosis of various types of cancer, 1953-1957 over 1943-1952.

In contrast to the above, all diagnoses of thyroid carcinoma between 1943 and 1955 were confirmed on review of the pathological material. Thus, possible differences in pathological interpretation can have no influence on the group 2 statistics. No significant differences were noted in histopathology of the group 1 cancers removed during the two periods (table 1). Whatever its pathogenesis, the increase in thyroid cancer was not selective. A similar pattern of diagnoses for the group 2 cancers has likewise been found for the two time periods (table 2).

Since 1954, patients with nodular goiter have been selected for surgery in a way that would increase the percentage of group 1 cancers; i. e., to recommend operation mainly for those patients in whom something more than the mere presence of a nodule suggested cancer. Three to four per cent seems to be an irreducible minimum, and without

TABLE 1.—*Pathological Diagnosis of Group 1 Thyroid Cancer*

	1943-1952		1953-1957	
Cell Type	No.	%	No.	%
Papillary	7	37	21	37
Papillary and follicular	1	5	12	21
Follicular	8	42	18	31
Malignant adenoma	2	11	5	9
Undifferentiated	1	5	1	2

selectivity also a maximum. The results of our previously described method of selection[3] are presented in table 3. The number of thyroidectomies per 100,000 professional visits has steadily declined but the number of group 1 cancers has progressively increased. We have already presented a partial explanation of this phenomenon, although it is also possible that a real increase in the incidence of the disease has been a factor.

In table 4 are shown comparative observations of the two time periods that are of interest. During the second period, 11 times more thyroid nodules, ultimately diagnosed as cancer, were discovered during physical examinations performed for unrelated complaints. Casual observations support the interpretation that better criteria for surgical reference, rather than improved physical diagnosis, were responsible for the improved selectivity. Again, an actual increase in the disease is not ruled out. The size of cancers in group 1 was smaller for the second period, the nodules were apparent for a shorter length of time, and, as in the first period, they were largely asymptomatic. The presence in

TABLE 2.—*Pathological Diagnosis of Group 2 Thyroid Cancer*

	1943-1952		1953-1957	
Cell Type	No.	%	No.	%
Papillary	6	40	9	33
Papillary and follicular	4	27	6	22
Follicular	2	13	7	26
Malignant adenoma	1	7	0	
Undifferentiated	2	13	4	15
Lymphoma	0		1	4

the series of 10 cancers that were, in essence, accidental findings, raises the possibility that benign nodules are indicators of malignant ones. As noted before, operations on palpably normal glands should yield a pathological diagnosis of cancer of the thyroid in 2%. On this basis, 12 occult cancers would be expected in 636 thyroidectomies and the number of 10 is not unreasonable.

We note the incidence of cancer in surgical specimens increased from 4 to 15% during the present

TABLE 3.—*Incidence of Group 1 Thyroid Cancer in Patients with Nodular Goiter*

Yr.	Thyroidectomies per 100,000 Professional Visits	Total No. of Thyroidectomies	Total Cancers	%
1943-1952.....	15	438	19	4.3
1953	46	167	6	3.6
1954	34	125	7	5.6
1955	32	131	14	10.6
1956	25	111	15	13.5
1957	22	102	14	13.7

study. This latter figure parallels those of 10 to 30% usually cited in the surgical literature. That this agreement is brought about by a comparable degree of selection is suggested by a reverse trend reported from the Ochsner Clinic.[4] In their 1942 to 1949 series of patients operated on for solitary thyroid nodules, the incidence of cancer was 19.8%. In a later series from 1949 to 1956 the incidence was 3.9%. This unusual change might be interpreted as follows: In most areas, the surgical enthusiasm generated by the reported high incidence of thyroid cancers in patients with nodular goiter led to a decreased selectivity. The dictum of "remove all nodules" should lead to a cancer incidence of 3 to 4% in operated cases.

The number of operations for nontoxic nodular goiter almost tripled from one observation period to the next, but the age distribution of the patients so operated remained surprisingly constant. In table

TABLE 4.—*Comparative Observations for Group 1 Thyroid Cancer*

	1943-1952		1953-1957	
	No.	%	No.	%
Total no.	19		56	
Discovered on routine physical examination	2	10	22	40
Asymptomatic	13	68	48	84
Over 2 cm. in size	11	58	19	37
Cancer not palpable	1	5	7	12
Small cancer focus in large nodule	3	15	3	5
Lesion present 1 yr. or more	17	90	35	60
Av. age if over 1 yr.	5.5 yr.		3.5 yr.	

5 the increase appears evenly distributed throughout the age range. The number of cancers discovered, however, increased disproportionately in the younger age groups with only 15% of group 1 cancers being found in patients under 40 years of age for the period 1943 to 1952. A comparative figure of 55% for the later five-year period indicates

either greater medical significance was attached to nodules found during this time or a real increase occurred in the incidence of the disease.

The factor of selectivity, of course, is of no consequence in the increase in number of group 2 cancers. The comparative clinical features do not throw appreciable light on the reasons for the increase in this group (table 6). Although the youth movement evident in the group 1 statistics is not nearly so striking here, nevertheless, only one patient with group 2 cancer was diagnosed under the age of 20 in the early period, while six were seen in the last five years.

TABLE 5.—*Age Distribution of Patients Operated on for Nodular Goiter and for Group 1 Thyroid Cancers, by Percentage*

Age, Yr.	1943-1952 Thyroidectomies	Group 1 Cancer	1953-1957 Thyroidectomies	Group 1 Cancer
10-19	1	15	1	55
20-29	8		9	
30-39	22		26	
40-49	28	85	28	45
50-59	30		25	
60-69	10		9	
70-79	1		1	

Better public education as to the significance of lumps anywhere in the body may have been responsible for increased numbers of self-referrals of patients with cancers that were still 10 years to a lifetime away from clinical significance. This was not evident in breast cancer, however, another lesion presenting as a lump.

In table 7, relative values have been assigned to the various factors possibly significant in the increase of both group 1 and group 2 cancers. The values are obviously approximate and subject to considerable statistical error. The increased number of patients with group 1 cancers can probably be explained without postulating an increase in the incidence of thyroid cancer in the general population. The present study, however, does not completely eliminate this possibility, and we believe that further careful analysis of this aspect is essential. Whether factors other than those of changing institutional practice, public education, and chance account for the increased number of patients with group 2 cancers is more difficult to decide. Here again, definite evidence is lacking, but the figures more strongly suggest a real increase in thyroid cancer. Since the total number is small, a more definite statement is unwarranted. In this age of preventive surgery, it is important not to perform wholesale thyroidectomies because of a statistical increase in the incidence of thyroid cancers. This increase may be more apparent than real and to needlessly raise surgical morbidity would be contrary to medical aims. It is equally important, however, not to blind ourselves to the possibility that a true increase in incidence of thyroid cancer might considerably alter the approach to any program of selection of cases of nodular goiter for surgical treatment.

TABLE 6.—*Comparative Observations for Group 2 Thyroid Cancer*

	1943-1952		1953-1957	
	No.	%	No.	%
Total no.	15		27	
History of goiter of over 1 yr.	1		5	
Thyroid normal to palpation	7	46	10	38
Palpable regional metastases	11	73	15	58
Distant metastases	3	20	7	23
Under age 40	7	47	12	44
Under age 20	1	7	6	22

Summary

A significant increase has been observed in the incidence of cancer in patients with thyroid malignancy. For the patients with a clinically undiagnosed thyroid cancer, qualitative and quantitative changes in patient population, greater number of operations for nontoxic nodular goiter, and improved clinical selection may account for most of the increase. The increased number of frank thyroid cancers is more difficult to explain on such grounds and suggests that the incidence of thyroid cancer in the general population is increasing. Physicians should regard the approach to preventive surgery of thyroid cancer as being in a dynamic state.

TABLE 7.—*Summary of Factors Considered Responsible for the Observed Increase in Thyroid Cancer*

	Group 1	Group 2
Institutional growth	8%	15%
Institutional prestige	2%	30%
No. of thyroidectomies	30%	0
Changing pathological criteria	18%	0
Improved clinical selection	20—?	0
Increased self-referral	?	?
Increased incidence in the general population	?	?

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SURVIVAL RATE OF PATIENTS WITH BREAST CANCER IN A SMALL COMMUNITY

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Halsted's first published report in 1907 [1] showed a five-year salvage rate of 28.9% for patients with breast cancer. This has been followed by many other reports, all showing an increasing survival rate. This trend is best shown in results obtained at the Massachusetts General Hospital and the Presbyterian Hospital of New York from 1911 to 1942.[2] The former shows an increase of 27 to 51%, while the latter is almost identical. The current five-year salvage figures for patients with breast cancer from a number of major teaching centers are summarized in table 1.

The wide variation in results may reflect the types of cases included as much as the mode of therapy. Nevertheless, Urban [3] stated that "most American clinics report a five-year salvage rate of about 55% at present" and supported this with a 54% rate for 800 cases from 1945 to 1948.

Whatever the most representative figure may be, it would seem logical for each community or institution to determine its own results in patients with breast cancer. It may be comforting to extrapolate a 55% survival rate to one's own hospital, but it is scarcely realistic. Many hospitals, and even whole communities, can never assemble the formidable numbers of cases that a major institution can in a year or two. Nevertheless, it is not unreasonable for a hospital or medical community to assess the results of its own cases, no matter how few, gathering whatever consolation or remorse the figures may offer when they are compared to established standards.

An attempt was made to collect data on the cases of breast cancer seen by local physicians in this area from July, 1947, through December, 1958. It was hoped this might answer the question "What happens to breast cancer patients in the Fredericksburg area?"

Materials and Methods

The Mary Washington Hospital serves the city of Fredericksburg, Va., and the surrounding area, with a present medical drawing population estimated at 50,000. Most of the surgical procedures were done by three surgeons, all of whom have been certified since the close of World War II. Case data were collected by surveying old operative log books, surgical pathology sheets, and death certificates and by contacts with the local physicians. One hundred three cases of breast cancer are known to have been seen by area physicians in the 11½-year period covered.

From the Pathology Laboratory, Mary Washington Hospital.

The 37% over-all survival rate revealed in this survey of 100 patients offers little evidence that significant progress has been made since the first such study was published by Halsted in 1907. Even when the figures are corrected to produce a 47% rate, there is little reason for complacency. It would seem logical for each community or institution to assess its results, no matter how few the cases, gathering whatever consolation or remorse the figures may offer when they are compared to established standards.

Results

The current status of 100 of the 103 patients has been determined. Assuming the three lost patients to be dead of disease, then 59 patients are determined to have lived five years or more or to have died in less than five years.

Five-year Survival Rates.—The five-year survival rates are shown in table 2. Of the 59 patients 22 lived at least five years, for a 37% over-all survival rate. If the three "lost" cases are not included in the total, the five-year survival rate then becomes 39%. Ten patients were obviously inoperable on the face of the chart and were subjected to biopsy or palliative mastectomy. Four received no surgical treatment. If these 14 cases are excluded, 45 operative cases remain, and 21 patients, or 47%, survived five years. If the three "lost" cases are deleted, the operative five-year rate then becomes 50%. Of 68 patients with known results 41, or 60%, lived three years.

The age distribution, duration of symptoms, and size of lesions are shown in table 3. In 33 cases, or 46%, the axillary nodes showed evidence of metastases. In 42 cases, or 54%, they did not. Radical mastectomy was performed in 74 patients and simple mastectomy in 19. The relationship of axillary metastases to survival is shown in table 4. Of 15 patients undergoing simple mastectomy 4, or 27%, survived 5 years.

Comment

To have meaning any survival figures must be measured against the unmodified course of the disease. Daland's [4] 100 untreated cases are generally accepted as representing the natural history of breast cancer. Shimkin [5] has collected other untreated series of cases and incorporated the results graphically. All show about 20% five-year and 35 to 40% three-year survival rates. If this is accepted as a line of departure then one may conclude that the 37% over-all survival rate in the Fredericksburg

area represents a favorable influence of treatment. This result differs but little from the 35.5% over-all rate at the University of Pennsylvania [6] and the 39.6% over-all rate from the Memorial Center between 1935 and 1942.[7]

TABLE 1.—*Representative Five-year Survival Rates for Patients with Breast Cancer*

Location or Institution	Operative Rate	Over-all Rate
Presbyterian Hospital, No. 4 (Haagensen, C. D.: Am. J. Roentgenol. **62**:328, 1949)	47.2	.....
Memorial Center for Cancer and Allied Diseases (Adair [7])	54.3	39.6
University of Pennsylvania (Miller and Pendergrass [8])	49.7	35.5
New York state survey (Burdick and Chanatry [12])	43.0	.....
Cleveland Clinic (Robnett, A. H., and others: Cancer **3**:757, 1950)	47.7	.....
University of Michigan (Bryant and others [10])	58.0	.....
Scotland (McWhirter, R.: Brit. J. Radiol. **28**:128, 1955)	58.0	42.0

When only the operable cases are considered the survival rate reaches 47%, slightly more than was found in another small series [8] but less than the 51% obtained in a collection of 49 cases.[9] Various centers report five-year survival rates of 49.7%,[6] 54%,[3] and 58%.[10] The three-year survival rate of 60% is little different from the 62% found at the Memorial Center.[3]

The 62% five-year survival rate of patients reported as having no metastases to the axillary nodes is less than the 75% considered attainable.[11] This suggests that pathological or surgical dissection was inadequate. If the fault were with the former it would have no bearing on the over-all operative results but would only change the grouping. Less than half the cases were reported to show such metastases, quite the reverse of the expectation. This, too, would indicate deficient pathological or surgical dissection. The New York state survey [12] also found an equal distribution of lymph node metastases. Here, also, large numbers of protocols did not comment on the state of the nodes.

TABLE 2.—*Five-year Survival Rates of Patients with Breast Cancer in Area of Fredericksburg, Va., 1947-1958*

Rate	No. of Cases	Living	Dead	5-Yr. Survival, %
Over-all	59	22	37	37
Corrected over-all	56	22	34	39
Operative	45	21	24	47
Corrected operative	42	21	21	50

The duration of symptoms prior to seeking treatment did not differ significantly from the New York state findings. The size of the lesion is also a crude index of duration, and the distribution of lesions according to size did not vary greatly from the expectation.[13] Both of these factors indicate that patients in this area are not being seen, on the average, much later than elsewhere. Of those surviving five years 80% reported for treatment within a month of discovering the lump, while of those dying in five years only one-third were seen within a month. (Race did not seem to be a factor in seeking treatment; 18% of the patients were Negroes,

TABLE 3.—*Age, Duration of Symptoms, and Size of Lesion in Patients with Breast Cancer*

	Cases	
Age, Yr.*	No.	%
20-30	6	6
30-50	40	40
50-70	34	34
over 70	19	19
Duration†		
1 wk.or less	14	17
2 wk.	14	17
1 mo.	17	20
3 mo.	8	9
6 mo.	10	12
1 yr. or more	21	25
Size, Cm.‡		
Less than 1	15	18
1-2	16	20
2-4	29	36
Over 4	20	25

* n = 99
† n = 84
‡ n = 80

about the percentage of the Negro population in the area.)

The 103 cases are felt to represent nearly all of the breast cancer occurring in the area in the past 11½ years. All patients treated in the hospital and all patients dying in the hospital or in the city limits are included. Death certificates from the counties are not filed locally. However, one county has no physician and patients are treated by Fredericksburg physicians. The other county has two physicians, one of whom has seen no breast cancer in the past 10 years. Conversation with local physicians has revealed only two or three additional cases which, because of lack of information, are not included. No doubt occasional patients may die at home of, or with, untreated breast cancer. Six patients had surgery done elsewhere, but these were all known to, and their progress followed terminally by, local physicians. If the average medical population of the area over the past 11 years is taken at 35,000, then the annual incidence would approximate 28 cases of breast cancer per 100,000 population. This is not far from the 30 per 100,000 population incidence reported in New York state.[14] The

TABLE 4.—*Relationship of Axillary Node Metastases and Survival in Thirty-three Patients with Breast Cancer*

Metastases	No. of Cases	5-Yr. Survival	
		No.	%
Yes	17	6	35
No	16	10	62

collected cases may represent at least 90% of all cases that have occurred in the area.

It would be interesting to know what other small medical communities achieve in the treatment of breast cancer. Certainly the local over-all salvage rate of 37% offers little comfort. Even when the figures are corrected so as to produce a 47% rate of

operative salvage there is little cause for complacency, since patients continue to die of the disease after the five-year mark. Perhaps it is wrong to regard Daland's 20% five-year survival rate as the therapeutic base line. Indeed, Collins [15] stated that "approximately 40% of breast cancers either grow locally and can be completely removed or grow so slowly that more than five years are required for recurrences to become manifest."

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CHRONIC THYROIDITIS IN CHILDHOOD

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Diffuse enlargement of the thyroid gland, low protein-bound iodine value, and the appearance of a nodule in one lobe of the thyroid in an 11-year-old girl led to the diagnosis of thyroid disease with the possibility of carcinoma. At operation the entire gland was found to be diffusely enlarged to about three times normal size. Enough tissue was removed for microscopic study to reveal striking alterations of the follicular architecture. The pathological diagnosis was acute and chronic nonspecific thyroiditis. Records of only 31 comparable cases have been found in a search of the literature. The patient was treated postoperatively with thyroid extract. Six months after operation the patient was receiving a maintenance dosage of 64 mg. of thyroid extract per day; she appeared clinically euthyroid, and the protein-bound iodine value was normal.

Chronic thyroiditis is a relatively rare cause of goiter in children. Only 31 patients with this disorder have been found after a search of the literature. Most of the diagnoses were made after operation for a goiter which was causing pressure symptoms or because carcinoma could not be ruled out in a nodular goiter. In only a few instances was the diagnosis suspected clinically and confirmed by needle biopsy. On the other hand, Winship,[1] in 1956, was able to collect data on 334 patients under 15 years of age with thyroid carcinoma. It is obvious that chronic thyroiditis is a much more unusual cause of goiter in this age group. To reemphasize thyroiditis, case histories of previously reported patients are reviewed below and the history of an additional patient is presented in detail. With the advent of newer diagnostic techniques, nonoperative diagnosis may be made if thyroiditis is considered.

From the Department of Medicine and the Whitehead Department of Surgery, Emory University School of Medicine.

Report of a Case

An 11-year-old girl was seen in the Emory University Clinic on July 21, 1958. Her illness had begun in December, 1954, when she was noted to have mild exophthalmos. There were no other signs or symptoms of thyrotoxicosis. A basal metabolic rate was −15%. Subsequently, her exophthalmos did not change, and she showed no evidence of thyroid dysfunction. In October, 1957, a diffusely enlarged thyroid gland was noted, and the protein-bound iodine value was 3.8 mcg. %. She appeared to be euthyroid. There were no pressure symptoms. In June, 1958, a nodule was discovered in the left lobe of the thyroid gland. Chest x-ray showed normal results. There was no history of irradiation to the thymus or tonsils.

Physical examination revealed a healthy, well-developed, preadolescent girl. The pulse was 88 per minute and the blood pressure 108/66 mm. Hg. There was slight widening of the palpebral fissures but no exophthalmos. There was no evidence of hyperthyroidism or hypothyroidism. The thyroid gland was three times normal size bilaterally, quite firm, slightly fixed, and nontender. There was an indefinite 1-cm. nodule in the left lower pole, with adjacent enlargement of the isthmus to 1 cm. in diameter. In the right lower pole there was a smaller ill-defined nodule. Two centimeters above and lateral to the left upper pole was a solitary 1-cm., firm, movable, nontender lymph node. The clinical impression was possible thyroid carcinoma.

Laboratory studies showed a hemoglobin level of 12.9 Gm. %. The sedimentation rate was 14 mm. per hour (Westergren); white blood cell count was 5,100 per cubic millimeter, with differential count of 51% segmented neutrophils, 41% lymphocytes, 5% eosinophils, and 3% monocytes. The chest roentgenogram was normal.

The protein-bound iodine value was 3.2 mcg. %. The 24-hour uptake of radioactive iodine (I^{131}) was 8.5%. The scanogram of the thyroid showed most of the I^{131} concentrated in the nodular areas (fig. 1).

On July 30, 1958, an operation was performed. The entire thyroid gland was diffusely enlarged to about three times normal size. The left lower pole and isthmus were larger than the remaining gland. The thyroid gland was firm, and no definite solitary nodules were found. The entire structure had a picture of nodularity. The gland was adherent to the pretracheal muscles and trachea. There was one large pretracheal lymph node, 1 cm. in diameter, superior to the isthmus, and there were numerous enlarged lymph nodes inferior to the isthmus, extending into the superior mediastinum. Several of these lymph nodes were removed and on frozen section revealed hyperplasia with no evidence of malignancy. Since the predominant disease was located in the left lower pole and the isthmus, this portion of the thyroid gland was removed and submitted for pathological studies. A definite diagnosis of a malignancy or a benign process could not be determined from frozen section studies, so it was decided to discontinue surgery at this point until permanent sections were completed. Because of the patient's age and possibility of thyroiditis and future development of hypothyroidism, it was felt desirable to remove only enough tissue at this time to establish a diagnosis.

The pathological description was supplied by the department of pathology, Emory University Hospital. The specimen consisted of thyroid tissue weighing 4 Gm. and measuring 2.2 by 1.5 by 0.5 cm. The external surface was irregular and transmitted a grayish-red color with moderately accentuated vascularity. The consistency of the tissue did not

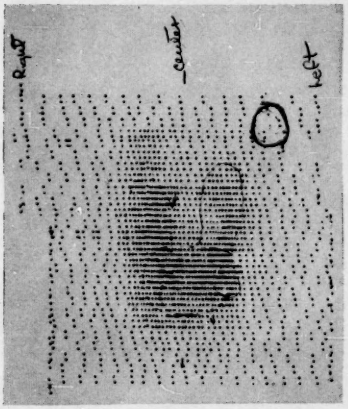

Fig. 1.—Radioactive iodine concentrated in lower left pole and isthmus. Enlarged cervical lymph node is circled at upper right.

appear remarkable, although there was a suggestion of nodularity. On cut surface the tissue had a yellowish-pink color and appeared divided into many small lobulations 2 to 3 mm. in diameter. Separately submitted were six lymph nodes measuring up to 0.5 cm. in diameter. These were unremarkable in consistency and had a homogeneous glistening grayish-yellow cut surface. On microscopic examination the architectural pattern of the thyroid tissue was markedly distorted (fig. 2).

There was a distinct nodular pattern, the nodules being separated by thin bands of connective tissue. Within each nodule considerable variation in pattern was observable. The most striking alteration was that of the follicular architecture, which in many areas took on a distinctly papillary configuration and in other areas appeared to form large

anastomosing channels. In most areas the epithelium was tall cuboidal or columnar, and small amounts of colloid were present. In other areas there was cystic dilatation of follicles with a flat epithelium and the accumulation of large amounts of thin staining colloid. In a few areas the thyroid tissue appeared to have undergone considerable atrophy and replacement by fibrous tissue. In most of the nodules there was striking interstitial infiltration of lymphocytes, plasma cells, and mononuclear phagocytes, and in several areas distinct lymphoid follicles were seen. Despite the marked variation in the appearance of the follicular epithelium and its tendency to a papillary configuration, the follicular cells appeared remarkably uniform in all areas and showed very little evidence of proliferative activity. The separately submitted lymph nodes

Fig. 2.—Section showing dilated follicle with flat epithelium and infiltration with lymphocytes and mononuclear phagocytes forming lymphoid follicles.

showed some hyperplasia of the lymphoid follicles and a moderate degree of subacute and chronic lymphadenitis. The pathological diagnosis was subacute and chronic nonspecific thyroiditis.

The immediate postoperative course was uneventful. The patient was seen four weeks after operation. The operative site was well-healed, and the remaining thyroid tissue was unchanged. The deep tendon reflexes showed slight prolongation of the relaxation phase. Therapy with thyroid extract, 32 mg. daily, was begun. This was increased to 64 mg. daily in a few weeks. Six months after surgery the patient was clinically euthyroid and the residual thyroid tissue was unchanged. The protein-bound iodine value at this time was 6.4 mcg. %.

Comment

It is difficult to determine the relative occurrence of this lesion in children, as there are so few reports. Pemberton and Black [2] reviewed the cases of 52 children, 14 years old and under, who were operated on for nontoxic nodular goiter at the Mayo Clinic from 1908 through 1943. They found only two patients with thyroiditis. Of the remaining 50, 32 had adenoma and 18 carcinoma. Norris and Pollock [3] reported their experience over an 18-year period at Los Angeles Children's Hospital. Of 14 children operated on for nontoxic goiter, 2 girls, aged 7 and 10, had typical struma lymphomatosa (Hashimoto's struma), 9 had adenomas, and 3 had malignancy.

Crawford [4] states that one-half of the patients with nontoxic goiters seen in the Pediatric Endocrine Clinic at Massachusetts General Hospital have either adolescent goiters or chronic lymphocytic thyroiditis (Hashimoto's disease). These patients are nearly all female, from ages 9 through adolescence. Thus, it would seem that thyroiditis is not uncommon in the experience of this clinic. On the other hand, Buxton [5] described only 2 patients among 173 with nontoxic goiters studied at the University of Michigan and the University of Maryland. In one the gland was diffusely enlarged, and in the other it was a solitary nodule. Only 18 patients in this group had nodular goiters.

Since the classic description of the two major types of chronic thyroiditis by Riedel and Hashimoto, much interest has been shown in this group of diseases. Excellent reviews [6] of the subject have been written but are beyond the scope of this discussion.

In 1938, the first reports of struma lymphomatosa occurring in childhood were made by Hellwig [7] and others. Joll,[6b] in his excellent Hunterian lecture in 1939, mentioned a 10-year-old girl. Only isolated reports were made until Statland's [6c] summarized 51 cases of struma lymphomatosa from Massachusetts General Hospital, in which three young girls were studied.

The most complete study of this disorder in children is that of Gribetz and others.[8] They described six adolescent and preadolescent girls with firm goiters which were two to four times normal size and granular or nodular. The Delphian node or pyramidal lobe was enlarged in all instances.

Our patient exhibited several features of this disorder in common with features of others already reported in the literature. A long history of goiter was frequently reported. Enlargement of the thyroid had been present for an average of four years, ranging from seven months to eight years. In a few there was slow progression of the goiter, with a sudden increase in growth rate in the months before definitive therapy was started. The average age at

which a goiter was first noted was 9 years (in 15 patients). The majority of the patients, 27 of 31, were female. On examination, the thyroid was generally quite firm, three to four times normal size, with nodularity or lobulation by palpation. These characteristics have been described in 20 of the 31 patients previously reported. Although thyroiditis is a diffuse process, the surface of the gland tends to be irregular or nodular. In only one instance has the thyroid been reported as being diffusely enlarged with a smooth surface. Two patients presented clinically as having only a solitary nodule.

Because of the firm consistency, nodularity, and the frequent occurrence of cervical adenopathy, the diagnosis of carcinoma is often considered. However, thyroiditis is a diffuse process and usually causes enlargement of the entire gland. On the other hand, patients with early carcinoma usually have a solitary nodule or enlargement of a portion of the gland.

The symptoms are related to the local effects of a goiter. These are a sense of fulness or pressure, mild dysphagia, or hoarseness. Most of the patients are clinically euthyroid or only mildly hypothyroid. In only one instance has severe myxedema been present.[8] However, surgical procedures hasten the onset of hypothyroidism, probably in two ways: (1) by removal of functioning tissue and (2) by further release of antithyroid antibodies.

As yet, there is no laboratory test which may be considered specific, but several of the routine tests of thyroid function may be suggestive, if used in combination. The radioactive iodine uptake and serum cholesterol level are usually within normal limits. The basal metabolic rate is usually low-normal or low. In five cases where this test was done, values have ranged from −6 to −25%. However, the finding of a low basal metabolic rate and an elevated I^{131} uptake is quite suggestive.

Gribetz and others[8] and Skillern and others[6d] have noted an abnormal discrepancy between protein-bound iodine and butanol-extractable iodine values. In several patients the protein-bound iodine value was elevated while the butanol-extractable iodine value was normal or low. They felt that this was due to a disorder of synthesis and release of thyroid hormone, liberating calorigenically inactive substances into the blood stream. This situation was reversed in all patients by the administration of thyroid hormone, which also caused a decrease in the size of the goiter in most.

Although the radioactive iodine uptake alone is not helpful, failure to increase it after administration of thyrotropin is suggestive of thyroiditis, according to the studies of Skillern and others.[6d] This would indicate that the failing gland is already under maximal stimulation by thyrotropin. Also, the histological changes noted in the acinar epithelium of eosinophilia and high cuboidal structure are those associated with stimulation by the thyrotropic hormone. Thus, it might be expected that the areas most involved might concentrate more radioactive material. In our patient the scanogram showed this to be true. Since toxic nodular goiter has not been reported in children, a differential study in children with nodular goiter may be worthwhile. Most malignant nodules concentrate less iodine than the surrounding thyroid tissue.

The "era of immunology" in thyroiditis began in 1954 with the report, by Cooke and Wilder,[9] of an abnormal serum colloidal gold curve in two patients with struma lymphomatosa. Skillern and associates[6d] demonstrated abnormal colloidal gold curves in 20 of 25 patients. They showed that this finding was due to abnormal distribution of plasma proteins—low or low-normal albumin levels, elevated gamma globulin levels, and low or low-normal alpha globulin levels. They theorized that these findings were due to primary failure of the thyroid gland with thyroxin deficiency, because the gamma globulin level is low in toxic diffuse goiter (Graves' disease) and the abnormalities in plasma protein values and colloidal gold flocculation were corrected by the administration of thyroxin or thyroid extract. They also found abnormalities in other flocculation tests which are related to elevated gamma globulin–thymol turbidity, zinc sulfate turbidity, and cephalin-cholesterol flocculation.

In a series of excellent experiments, Witebsky[10] and associates made several valuable discoveries concerning the organ specificity of extracts of thyroid glands in a variety of animals. 1. Thyroid extracts act as antigens which are capable of eliciting organ-specific antibodies against the thyroid gland. 2. Rabbits injected with extracts of their own thyroid gland produce true autoantibodies. 3. Microscopic changes in the glands of the animals in which antibodies are produced are similar to those seen in chronic thyroiditis.

Roitt and associates[14] have demonstrated precipitin antibodies against extracts of human thyroid gland in a large percentage of patients with chronic lymphocytic thyroiditis (Hashimoto's disease). They have also shown that the active antigen is probably thyroglobulin. Paine and others,[10c] on the other hand, were unable to find antibodies in 14 patients with a surgical or needle biopsy diagnosis of chronic lymphocytic thyroiditis. However, they did find elevated antibody titers in 14 of 18 patients with a histological diagnosis of chronic nonspecific thyroiditis.

If the gland is diffusely enlarged, needle biopsy is a good diagnostic technique. In the presence of a solitary nodule, it is unwise to rely on needle biopsy, as the changes of chronic thyroiditis may be found adjacent to carcinoma. Nearly all solitary nodules should be surgically excised for study. If there is still doubt after all studies have been performed, then surgical biopsy should be done to establish a definite diagnosis.

Treatment

After the diagnosis of chronic thyroiditis is established, therapy with thyroid extract should be started, whether the patient is hypothyroid or euthyroid. This will suppress thyrotropin activity if used in adequate dosage, usually 60 mg. to 240 mg. daily.[6d]

The administration of thyroid extract in most patients with thyroiditis will cause a reduction in size of the goiter within three to six months. If there is a wide difference in protein-bound iodine and butanol-extractable iodine values, this will also be corrected.

If the thyroid is surgically explored, only a minimal amount of tissue should be removed for diagnosis. The isthmus may be removed to prevent pressure symptoms. The patient should then be placed on therapy with thyroid extract, as surgery seems to hasten the onset of hypothyroidism.

Thyroid extract should probably be continued indefinitely, for two reasons—first, to reduce the size of the goiter and prevent its recurrence and, second, to prevent the insidious onset of hypothyroidism in the adolescent. The only satisfactory way to determine the proper dosage level is by periodic determination of the serum protein-bound iodine level or butanol-extractable iodine level while the patient is on therapy with thyroid extract.[12]

Surgery may be necessary later for cosmetic reasons or to relieve obstructive symptoms, if thyroid therapy is ineffective. However, surgery should be delayed if at all possible, since thyroid extract therapy may require as long as a year to achieve reduction in the size of the goiter. Usually, maximal effect is achieved in three to six months.

Summary

Chronic thyroiditis is unusual in childhood and early adolescence. Only 31 cases have been found in the literature. There are usually no symptoms except for the presence of a goiter, but pressure symptoms may occur. If hypothyroidism develops, it does so late in the course of the disease. The gland is usually three to four times larger than normal, is firm, and may feel lobular or nodular. Most of the patients are female.

The diagnosis of chronic thyroiditis may be suspected on many clinical and laboratory bases: (1) a young female with a firm, nodular goiter and the findings of hypothyroidism; (2) an elevated protein-bound iodine level and relatively low butanol-extractable iodine level; (3) evidence of increased serum gamma globulin by serum electrophoresis and elevated serum colloidal gold flocculation, thymol turbidity, or zinc sulfate turbidity; and (4) the demonstration of specific antithyroid antibodies in the serum.

Needle biopsy or surgery may be necessary to establish a definite diagnosis. Once diagnosis has been made, the patient should be treated with thyroid extract in adequate dosage to maintain the protein-bound iodine level or butanol-extractable iodine level within normal range. Surgery may be necessary if an adequate trial of thyroid extract therapy proves ineffective in reducing the size of the gland and if pressure symptoms develop.

The histological description given for the patient in this study was made by Dr. Abner Golden, Department of Pathology, Emory University Hospital and Emory University School of Medicine.

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ESOPHAGEAL REPLACEMENT IN INFANTS AND CHILDREN WITH USE OF A SEGMENT OF COLON

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A segment of colon is considered best for operative substitution of a damaged esophagus because it resists peptic ulceration, it functions well during swallowing, and its blood supply remains intact after transposition. Before a child is considered a candidate for the operation, conservative treatment should be done (dilatation for esophageal stricture, portal-systemic venous anastomosis for varices). The operation was performed successfully on six of nine infants with congenital esophageal atresia, four children with strictures from ingested lye, two with persistent esophagitis, and three with bleeding varices. Failure of the operative procedure was the cause of death in one child; in the others the cause was undetermined or unrelated. The technical difficulties of the transposition are encountered in the infant, and these can usually be obviated by delaying the operation until the child is 1 to 2 years old.

There are numerous disease processes involving the esophagus which require partial or total esophageal replacement. In the pediatric age group esophageal replacement is done for one, or a combination, of the following reasons: (1) esophageal atresia without adequate esophageal substance for primary anastomosis, (2) caustic strictures, (3) peptic esophagitis with stricture formation or bleeding, and (4) bleeding varices when portal-systemic shunts have failed to control bleeding.

In the Boston Children's Hospital we have had experience with these four esophageal lesions, and there is good reason to believe that we will see an increasing number of children with bleeding varices who will need esophageal resection and replacement therapy.

A satisfactory substitute for the esophagus should meet the following specifications: 1. It must serve as a satisfactory conduit for food and fluids to reach the stomach so that the patient can maintain satisfactory nutrition without taking prolonged periods of time for each feeding or meal. 2. The conduit must be anatomically small enough so that pulmonary function is not interfered with during a feeding. 3. The substitute must be sufficiently resistant to peptic juices so that ulceration, stricture, or bleeding are not frequent complications. 4. Formation of the substitute esophagus must be technically feasible for replacement of part or all of the esophagus with adequate blood supply for both proximal and distal anastomoses. 5. Preferably, there should be no unsightly cosmetic deformity such as is encountered with a subcutaneous antethoracic type conduit.

In the early years of treatment of esophageal atresia, the formation of a subcutaneous conduit containing small intestine distally and a skin tube proximally was utilized in the salvage of these infants.[1] Antethoracic tubes of small intestine have also been used for caustic strictures.[2] Some of these procedures required multiple major operations and long periods of hospitalization. Anastomotic strictures were frequent complications, and the subcutaneous bulging of the anterior chest wall was cosmetically unsatisfactory.[3] Fistula formation, due to difficulty in maintaining the blood supply in the small intestine, which has rather short arcades, was not uncommon.

Plastic tubes have been used in the replacement of small segments of esophagus when carcinoma has been resected. These cannot be utilized for long segments, and there is a tendency for these tubes to leak at their anastomotic sites.[4]

The thoracic part of the stomach manifests well-known sequelae of peptic esophagitis and dyspepsia which are unpleasant and detrimental to the health of the patient.[5] In 1953 and 1954 we treated four patients with esophageal atresia who had inadequate esophageal length for primary anastomosis. These patients had the stomach mobilized and pulled into the chest for anastomosis to the short proximal esophageal segment. Three of these four patients died in the immediate postoperative period due to atelectasis or aspiration of vomitus. We consider this to be an unsatisfactory type of esophageal replacement because of both the high immediate mortality and the serious late sequelae.

Recently there has been a report of the formation of a tube from the greater curvature of the stomach, this being anastomosed to the esophagus via the suprasternal notch. We have had no experience with this but will be interested in the eventual results of such a procedure.

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Read before the Section on Surgery, General and Abdominal, at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 9, 1959.

At the present time we, along with others, have found the colon to be the most satisfactory replacement for the esophagus.[6] It is resistant to peptic ulceration, and it has a good blood supply which is anatomically arranged so that the marginal artery of Drummond can be utilized to supply a long segment of colon to replace the entire esophagus if this is necessary. Although the colon does not have purposeful propulsive peristalsis, most patients have no difficulty in eating fairly rapidly as long as they eat in an upright position. Since 1953 we have had the opportunity of treating 18 patients (see table) with colon replacement of part or all of the thoracic esophagus. This paper is a report of our experience with these cases, description of the technical aspects of the operation, present status of the procedure, and recommendations.

Indications for and Results of Coloesophagoplasty in Eighteen Patients

Indication	Living, No.	Dead, No.	Total
Esophageal atresia	6	3	9
Lye stricture	4	0	4
Peptic esophagitis	2	0	2
Bleeding esophageal varices	3	0	3
Total	15	3	18

Esophageal Atresia

The largest group of patients was those with esophageal atresia who had inadequate esophageal length for primary esophageal anastomosis. Nine patients with this anomaly have been treated by colon substitution. These patients usually do not have a tracheoesophageal fistula, so the primary procedure is that of exteriorization of the upper esophageal pouch so that saliva can drain out onto a dressing on the neck rather than constantly spilling over into the trachea, with resultant pneumonitis. A gastrostomy is then performed for feeding purposes until the esophageal replacement can be performed. Occasionally, in the patient with esophageal atresia and tracheoesophageal fistula the esophageal segments will be of inadequate length for primary anastomosis; then the tracheoesophageal fistula must be divided so that reflux of gastric juice into the trachea is prevented. When we first began using the colon as a substitute esophagus, the procedure was performed in the early weeks or months of life. Technical difficulties ensued which have led us to abandon this; we now wait until the child is approximately 20 lb. (9.1 kg.) in weight or 1½ years of age before we attempt the definitive procedure. The following is a typical case presentation.

Case 1.—This 3-day-old infant was admitted to the Boston Children's Hospital on Feb. 18, 1957, weighing 3 lb. 9 oz. (1,587 Gm.). Prior to admission it was noted that he regurgitated feedings through his nose. Subsequent roentgenograms revealed an esophageal atresia without tracheoesophageal fistula. Soon after the patient's admission, the upper esophageal segment was exteriorized in the neck and a Stamm gastrostomy was performed; both procedures were done with the patient under anesthesia with locally given procaine hydrochloride. On March 26, 1957, at the age of 6 weeks, the child weighed 5 lb. 15 oz. (2,693 Gm.) and was discharged from the hospital. The baby was fed by gastrostomy at home and was readmitted to the hospital on June 17, 1958, at the age of 16 months, weighing 24.5 lb. (11.1 kg.). After a succinylsulfathiazole (Sulfasuxidine)–neomycin sulfate preparation and cleansing enemas were given, the child underwent esophageal substitution with use of the ascending colon. Postoperatively, small amounts of saliva leaked through the cervical wound for two weeks and then stopped spontaneously. A roentgenographic study of the esophageal replacement made with barium revealed good function (fig. 1). The child ate well and gained weight.

It should be noticed that this child entered the hospital weighing 3 lb. 9 oz. The prognosis of premature infants with esophageal atresia is improved by minimal procedures necessary to protect the lungs and to allow alimentation. Any definitive procedure should be delayed until the child is gaining weight and is of adequate size to obviate technical difficulties inherent in the small patient. We now consider approximately 1½ years the ideal age for the definitive procedure in these infants.

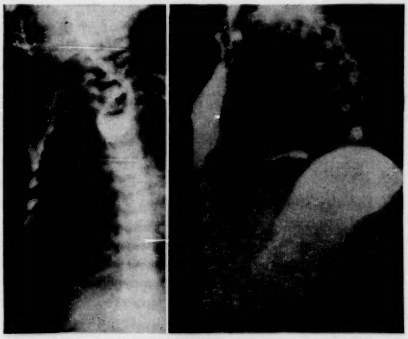

Fig. 1 (case 1).—*Left*, esophageal atresia without fistula. *Right*, retrosternal replacement of the esophagus with use of ascending and transverse colon.

Esophageal Stricture Secondary to Lye Ingestion

We have had four cases of caustic esophageal stricture which have been resistant to dilational therapy. The number of dilations in the four cases have varied between 23 and 100. Exactly how many dilations should be done prior to the recommendation of colon substitution is a matter of individual concern, and more emphasis should be placed on the frequency of necessary dilations

rather than the actual number of dilations. The degree of nutritional impairment is also a factor in this decision. The following case is an example of this type therapy in a patient who was resistant to dilational therapy because of extensive and severe stricturing.

CASE 2.—At the age of 2 years this child ingested lye. The patient had had two esophageal dilations prior to her admission to the Children's Medical Center six weeks after the lye ingestion. Esophageal dilation was impossible at that time due to the severity of the stricture; therefore, a gastrostomy was performed and a string was passed through the esophagus to facilitate retrograde dilations, with use of Tucker type dilators. During the ensuing 18 months, the child had 23 such dilations, and roentgenograms of the esophagus revealed involvement of practically its entire length. At this time it was felt that further dilations would not be effective except as a temporizing measure; therefore, on May 15, 1958, when the child was aged 4 years and 7 months, the esophageal stricture was bypassed with use of the right part of the transverse colon. A Heineke-Mikulicz pyloroplasty was performed at the same operation. Postoperatively, the child was able to swallow well; therefore the gastrostomy was closed two months later (fig. 2).

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Peptic Esophagitis

The majority of infants who have repeated episodes of regurgitation of fluids into the esophagus recover from this abnormal physiological state

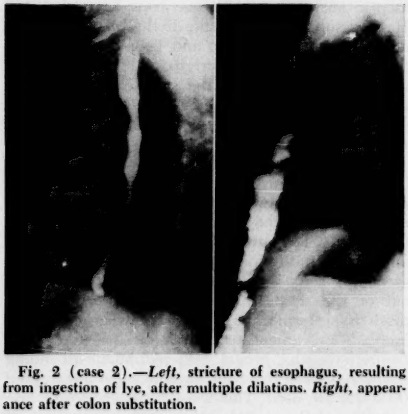

Fig. 2 (case 2).—*Left*, stricture of esophagus, resulting from ingestion of lye, after multiple dilations. *Right*, appearance after colon substitution.

spontaneously, provided they do not have central nervous system disease. The upright position seems to hasten recovery from this abnormality. Rarely these children do not improve, and some develop severe peptic esophagitis with ensuing stricture formation. We have had two such patients who have required resectional therapy; one of the cases is reported.

CASE 3.—This patient was first seen at the Children's Hospital in June, 1948, at the age of 4½ months because of recurrent vomiting and failure to gain weight. Esophagoscopy revealed severe esoph-

Fig. 3 (case 3).—*Left*, severe peptic esophagitis with stricturing. *Right*, partial esophageal replacement with colon.

agitis in the lower esophagus. The child was placed on an antacid regimen and was fed in the upright position; however, this regimen was not strictly adhered to at home. She was lost to follow-up and returned at 8 years of age with a very tight stricture of the lower third of the esophagus, which was quite difficult to dilate. She was anemic, and weighed only 36 lb. (16.3 kg.). Between June, 1956, and November, 1957, the child required six esophageal dilations, during which time she gained 16 lb. (7.2 kg.) but could still eat only puréed or very soft foods. On Jan. 9, 1958, she had resection of the lower one-third of her esophagus with interposition of the transverse colon between the proximal esophagus and stomach. This was performed through a left thoracoabdominal incision, and a new esophageal hiatus was formed through the left side of the diaphragm. Four months later the child required one dilation of the anastomosis; since that time she has been able to eat a regular diet without difficulty and is entirely asymptomatic (fig. 3). This syndrome is not common in the pediatric age group; however, when present, it causes severe nutritional inadequacies because of both dysphagia and blood loss.

Bleeding from Esophageal Varices

The preferable therapy for the patient with bleeding esophageal varices is some type of portal-systemic venous anastomosis. Since the majority of children with bleeding varices have portal vein thrombosis, splenorenal shunt is most commonly employed. If the child has had a previous splenectomy or if the shunt has thrombosed, then one is left only with a direct approach to the bleeding varices. This involves either suturing of the varices or resectional therapy of the affected esophagus and stomach. The following case presentation is of a child who had a splenectomy for congenital spherocytosis followed by bleeding varices. This then required direct attention to the varices.

CASE 4.—The patient was first seen in the Children's Hospital on Oct. 21, 1948, at the age of 12 days because of omphalitis. This was treated with

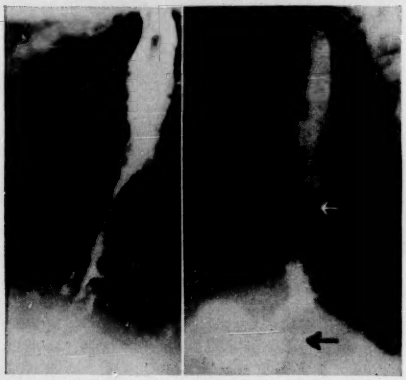

Fig. 4 (case 4).—*Left*, esophageal varices in patient who had previous splenectomy and ligation of esophageal varices with persistent bleeding. *Right*, colon interposition after resection of lower one-third of esophagus and upper one-third of stomach. Interposed section of colon is outlined between arrows.

antibiotics. The child improved and was discharged. At the age of 4 years he had a splenectomy for congenital spherocytosis. In October, 1956, at the age of 8 years, he vomited blood and was found to have esophageal varices. On Oct. 29, 1956, the esophageal varices were ligated with catgut and silk. During the ensuing two years, he had three minor hemorrhages; then on Dec. 25, 1958, he had an exsanguinating hemorrhage requiring multiple transfusions and esophageal tamponade. The child came close to death during this episode. On Dec. 29, 1958, he underwent resection of the distal third of the esophagus with replacement by transverse colon and pyloroplasty. Postoperatively, the pyloric canal was obstructed and required an anterior gastrojejunostomy. After this the child was able to eat a normal diet. He had no further episodes of bleeding (fig. 4).

In a patient who has no available veins in the portal system for shunting, resectional therapy offers the best chance of preventing recurrent life-endangering hemorrhage. Our experience with ligation of varices has been good only as a temporizing measure.

Technique

The technical approach to coloesophagoplasty depends on the amount of esophagus to be replaced or bypassed. The technical aspects of total thoracic coloesophagoplasty as it is now performed routinely in the Boston Children's Hospital will be described first. The patient is placed on the operating table in the supine position, with the head and neck extended. Preparation and draping include the entire abdomen as well as the chest and neck. The abdominal cavity is entered through an upper right paramedian incision. The omentum is removed from the transverse colon. The entire ascending colon, terminal ileum, hepatic flexure, and transverse colon are mobilized. The blood supply to the colon is visualized and careful attention given to the distribution of the midcolic vessels. Bulldog clamps are placed on the ileocolic and right colic vessels so that the colon can be observed for adequate blood supply from the midcolic vessels. The terminal ileum is divided as is the left transverse colon distal to the midcolic arcades. The actual cautery is used for dividing the intestine, and continuity is reestablished by a closed-type aseptic anastomosis with one layer of interrupted Halsted sutures of 0000 silk. If the blood supply is adequate, the right colic and ileocolic vessels are divided close to their origin and the ascending colon is passed behind the stomach, through the hepatogastric ligament, and through a tunnel which has been formed by blunt dissection behind the sternum.

While this is being done, another operating team has made a transverse incision low in the neck and dissected between the sternocleidomastoideus muscles, behind the trachea, and isolated the upper esophagus. The tunnel is then continued from above, and the terminal part of the ileum and the ascending colon are pulled through this tunnel and out of the cervical incision. A two-layer anastomosis is performed in the neck between the upper esophageal segment and the colon after the excess ileum, appendix, cecum, and redundant ascending colon have been removed. Two layers of interrupted 0000 silk are used. This wound is then closed, and a drain is left near the anastomotic site in case of leakage.

The cologastrostomy is then performed with use of an open-type anastomosis with 000 running chromic catgut inside and interrupted 0000 silk outside. This is best performed on the lesser curva-

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ture of the stomach; it is not necessary to perform this anastomosis high, because this tends to kink the colon. A Heineke-Mikulicz pyloroplasty is then done to facilitate gastric emptying and to minimize reflux of gastric contents into the colon. A Stamm gastrostomy is done routinely for intestinal decompression and for feeding purposes during the immediate postoperative period. On previous occasions the colon has been passed through a new hiatus in the left leaf of the diaphragm and behind the left lung root, but at present we feel that the retrosternal position has the advantage of not entering the pleural cavity and also of giving a more direct route for the conduit (fig. 5).

If only the lower third of the esophagus is to be replaced, the following procedure is used. The patient is placed on the table in an oblique fashion so that the left anterior part of the chest and left side of the abdomen are uppermost. A thoracoabdominal incision is used through the seventh or

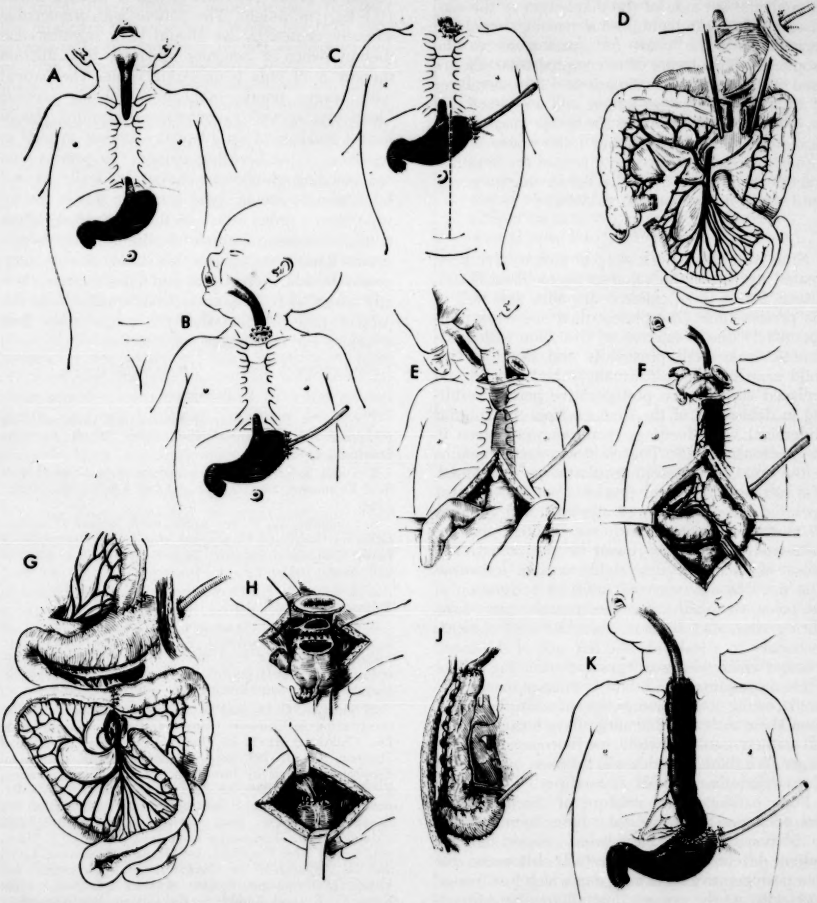

Fig. 5.—*A*, sketch of esophageal atresia at birth and, *B*, after marsupialization of esophagus and gastrostomy; *C*, outline of incision; *D*, mobilization and isolation of colonic segment; *E*, creation of retrosternal tunnel; *F*, mobilized colon within tunnel; *G*, reconstruction of intestinal continuity; *H and I*, details of esophagocolonic anastomosis; *J and K*, position of colon behind sternum with gastrostomy in place for decompression of intestinal tract.

eighth intercostal space. The inferior pulmonary ligament is divided, and as much of the esophagus as is necessary is dissected free for resection. The transverse colon is then freed of its omentum, and a segment of sufficient length is isolated with the midcolic vessels used for blood supply. Actual cautery is used for transecting the intestinal segment, and continuity is reestablished, with use of a closed-type aseptic anastomosis of Halsted sutures of 0000 silk. Either a new hiatus is formed through the left side of the diaphragm or the esophageal hiatus can be utilized in passing the colonic segment into the chest for anastomosis to the esophagus. Two layers of interrupted 0000 silk are used in the upper anastomosis and an inner layer of running 000 chromic catgut and an outer layer of interrupted 0000 silk in the lower anastomosis. Routinely, a Heineke-Mikulicz pyloroplasty is performed. A Stamm gastrostomy is used for intestinal tract decompression as well as for feeding purposes, until the child is ready to swallow.

Results

Nine patients with esophageal atresia have been treated by use of the colon as an esophageal substitute. Six of these children are alive and well at the present time. One patient died one week postoperatively due to necrosis of the colon with anastomotic leaks both proximally and distally. This child also had the gastrostomy tube removed and replaced early in the postoperative period, resulting in dehiscence of the stomach from the anterior abdominal wall; feedings therefore were given in the peritoneal cavity. This child was aged 3 months at the time the coloesophagoplasty was performed. The second fatality was that of a patient who was operated on at 12 days of age and died at home 10 months later. The death was sudden, and unfortunately no autopsy could be performed. The cause of death in this child remains unknown. The third fatality was the result of perforation of the colon, six months after the operative procedure, during attempted dilation. The child died of sepsis secondary to a leak into the left side of the chest. Another child who was operated on a the age of 2 months required revision of both anastomoses due to stricturing and torsion of the colon. In the recent cases these technical difficulties have been obviated by waiting until the child has become older and larger. We think that this will decrease our number of complications as well as fatalities.

Four patients with stricture of the esophagus due to ingestion of lye, who have been resistant to dilational therapy, have been operated on. One patient developed a small-intestinal obstruction due to a postoperative band adhesion which was treated surgically. At the present time all are able to swallow without difficulty and are much improved.

The two patients with peptic esophagitis and stricture formation can both swallow without difficulty. The three patients with esophageal varices have had no further bleeding episodes, nor is there any evidence of varices in the interposed colonic segment.

Summary

Utilization of a segment of the colon has been carried out in 18 patients requiring substitution for either a diseased or congenitally atretic esophagus. The definitive procedure for the patients with esophageal atresia should be performed when the patient is either 1½ years of age or at least 20 lb. (9.1 kg.) in weight. The patient with irreversible stricture caused by lye should have substitutional therapy when it becomes apparent that dilation therapy is of only temporizing value. The patient with severe peptic esophagitis causing chronic blood loss as well as nutritional crippling should have formation of an adequate conduit as well as resection of the bleeding source. The patient who has bleeding esophageal varices is ideally treated by a portal-systemic type shunt. If this is impossible, then a direct attack on the esophageal varices is the remaining alternative. In our experience, suture ligation of varices has been of only temporary benefit. Resectional and substitutional therapy seems to be a more rational approach. At the present time we feel that the colon is the best structure for esophageal substitution.

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EMOTION AND GASTRIC ACTIVITY

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The emotional responses of 24 men were observed before and after vagotomy for duodenal ulcers. The surgical treatment was necessitated by hemorrhage, intractable pain, obstruction, or combinations of these conditions. The observations included fluoroscopy, roentgenograms, and determinations of the acidity and volume of gastric juice. Emotions were aroused by stressful interviews which proceeded with minimum delay to the patient's personal problems. These interviews elicited the same overt signs of psychological distress after the operation as they had before, but they no longer caused the increases of gastric secretion and motility seen in subjects with intact vagi. Since vagotomy was followed by healing of the ulcer in every instance, these findings strengthen the conviction that emotional influences play a role in the causation of duodenal ulcer.

Emotional tension is frequently expressed in somatic dysfunction, particularly of the gastrointestinal tract.[1] Psychotherapy aimed toward reducing the incidence of emotional distress has been considered to be an important adjunct to medical and surgical therapeusis of duodenal ulcers. This is a study of the effect of emotional stress on gastric activities before and after surgical interruption of the parasympathetic innervation of the stomach by vagotomy. Psychotherapeutic procedures were not used in this study; the patients received only medical and surgical treatment for their ulcers, except for the psychological aspects of the experimental work involved.

It is well established [2] that acid gastric juice is a *sine qua non* for the development and maintenance of a peptic ulcer. A potent source of corrosive gastric acid is the vagally innervated fundus. A complete vagotomy appears to abolish the nervous phase of gastric function and to reduce the humoral phase of gastric secretion.[3] Many investigators have observed that the average patient with duodenal ulcer secretes more gastric acid than the normal person, and, what is more important, he secretes more when no obvious stimulant is present. For example, there is continuous secretion throughout the night, which appears to account for the night pain so frequent in such patients.[4]

It has been suggested by many authors [5] that emotional tensions operating on either an unconscious or a subconscious level play an important part in the etiology and chronicity of duodenal ulcers. It may be that much of the material which is successfully repressed during waking hours is psychologically freed in sleep to stir the emotions and acts as an additional stimulant to the autonomic nervous system. Overactivity of this system has many effects on the gastrointestinal tract, among which are hypersecretion, hypertonicity, and hyperperistalsis.

Method of Study

Experimental procedures were designed to study the immediate effect of stressful psychological interviews before and after vagotomy. Previous work in this connection by Wolf [11] and Wolff and Levine [4] involved actual visualization of the human gastric mucosa during stressful interviews. Their patients did not undergo vagotomy, however.

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The subjects were 24 men with duodenal ulcers selected at random from 150 persons referred for surgery after careful study by the medical and surgical gastroenterology services.

The criteria for such surgical referrals were hemorrhage, intractable pain, obstruction, or a combination of these conditions. The age range of the subjects was from 27 to 69 years. Duration of symptoms ranged from 1 to 30 years. The average period of hospitalization prior to surgical therapy was 2.8 months.

The patients were contacted individually previous to the experiment, and the general nature of the proposed procedures was described to them. Some ideas concerning the general problem areas of each patient were noted at that time, in order that the interviewer could proceed with minimal delay to the crux of the patients' difficulties during the period allotted for this phase of the study.

One day previous to operation a Levin tube was inserted nasally, under fluoroscopic observation, to be certain that the tube did not enter the duodenum. The hypersecretory tendency of patients with duodenal ulcer in the interdigestive periods (between meals and during the night) has been mentioned. This appearance of hydrochloric acid in the gastric juice is intermittent; in recognition of this periodic secretion it was realized that there might

be a fortuitous occurrence of "spontaneous" secretion after the introduction of an experimental procedure and that this might be interpreted erroneously as evidence of stimulation. Therefore, the interdigestive secretion was collected twice during the half-hour period just prior to the experiment and x-rays were taken. After this, two fasting gastric samples were obtained at half-hour intervals. The patient was then interviewed regarding emotionally charged personal problems. Each interview was geared individually in accordance with previous notes giving clues to problem areas. The third experimental gastric sample was withdrawn when overt evidence of psychological stress appeared to be optimal; e. g., pupillary dilatation, flushing or blanching, perspiration, tremors of lips or hands, restlessness, and other signs of tension. The patients invariably reported the presence of localized epigastric pain during most of this period, which occupied an average of 40 minutes. After 15 minutes of rest, a fourth sample was taken, fluoroscopy was done, and x-rays were taken. These procedures were repeated at two to three months and at one and one-half to two years after vagotomy. The gastric samples were checked for units of free acid and for volume. The statistical significances of preoperative and postoperative differences were estimated with use of a sign test.[6]

Results

Prior to vagotomy there was a reliable increase in gastric activity with emotional distress. Levels of significance obtained were free acid units $p = 0.0001$ and volume $p = 0.01$, indicating that the differences obtained were valid and were not chance occurrences. Motility and tonicity of the stomach increased noticeably, as evidenced by fluoroscopy and x-rays.

After vagotomy overt signs of emotional distress judged to be equivalent to that seen before surgery were easily aroused. There did not appear to be evidence of adaptation to problems; signs of physiological disturbance appeared at close to the same average time as previously. However, on questioning, there were no reports of epigastric pain. Neither free acid nor volume increased significantly at any of the trials. Radiologic evidence of decreased tonicity and motility of the upper region of the gastrointestinal tract was present.

The interview method of exciting emotional response appears to be a useful one in laboratory experiments of this type. It has the drawback of lack of standardization, but it has been found in this study and previously by Wolf [11] and his coworkers to have compensatory advantages.

Although patients, after vagotomy, reacted in a manner that was judged to be equivalent to their preoperative behavior as regards overt signs of psychological distress, the upper region of the gastrointestinal tract was not responsive and healing of the ulcer occurred in each instance.

Summary

The role of emotional tension in the etiology of gastrointestinal disorders is well established. A study was made of the role of such tension on gastric activities before and after surgical interruption of the parasympathetic innervation of the stomach by vagotomy.

Twenty-four men with duodenal ulcers were selected at random from 150 patients referred for surgical treatment. Ages ranged between 27 and 69 years and duration of symptoms from 1 to 30 years. A Levin tube was inserted nasally and x-rays were taken. Procedures were repeated at two to three months and at one and one-half to two years after vagotomy.

Samples were checked for free acid units and volume. The significance of preoperative and postoperative differences was estimated with use of a sign test. Prior to vagotomy there was a reliable increase in gastric activity with emotional distress. The motility and tonicity of the stomach increased noticeably as evidenced by fluoroscopy and x-rays. After vagotomy, overt signs of emotional distress judged to be equivalent to preoperative response were easily aroused. Neither the acid nor the volume increased significantly. Radiologic evidence of decreased tonicity and motility was present.

Although the patients reacted strongly to psychological stress in depth interviews after vagotomy, the upper region of the gastrointestinal tract was not responsive and healing of the ulcer occurred in each instance.

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MASTER TWO-STEP EXERCISE TEST IN CLINICALLY UNSELECTED PATIENTS

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The prognostic value of electrocardiographic tracings was investigated in the course of annual physical examinations of 756 business executives who had no history or symptoms suggestive of coronary heart disease. The age range was from 23 to 74 years. Electrocardiograms were obtained in each patient after the double Master two-step exercise test. The number of patients having abnormal electrocardiographic patterns when first examined was 280, and, of these, 32 later developed coronary artery disease. The remaining 476 had normal tracings, and only 20 developed coronary disease. The significant findings concerned the ischemic type of response pattern, which was found on 23 of the initial tracings. Sixteen (70%) of these patients later developed coronary artery disease. This finding is significant in view of published data on patients with known coronary disease, which show that 61.3% develop the ischemic pattern after the Master two-step test.

There have been many publications on the Master two-step exercise test in clinically selected patients. Most are selected because of various types of chest pain or other symptoms that suggest coronary artery disease. Others are selected because of known coronary disease, and the exercise test is done and then compared with results in known healthy persons to prove or disprove its accuracy. If a large group of clinically unselected patients can be accumulated and followed for an adequate period of time, the material resulting should aid significantly in determining the reliability of the various electrocardiographic changes and the prognostic value of the Master exercise test.

The majority of patients seen at the Greenbrier Clinic are there for a periodic health examination and not because of specific symptoms, so this clinic is in a particularly good position to accumulate a group of clinically unselected patients. However, it is only fair to say that there is considerable sociological selection, in that the majority of the patients seen are middle-aged male business executives. Only patients who were followed for at least three years from the time of the original Master two-step exercise test were used in this analysis, which in itself involves some selection, but not clinical selection. Some of the patients had had follow-up examinations for as long as 10 years, but the average period of follow-up was slightly over 4 years.

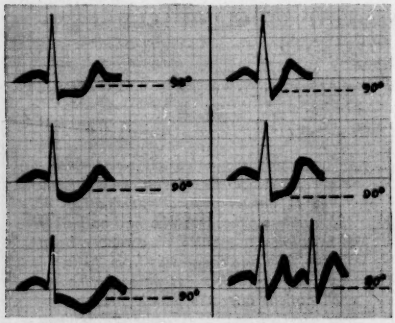
From the Greenbrier Clinic.

The Greenbrier Clinic does routine double Master two-step tests on all male patients. The method used is the standard 9-in. step as described by

Master,[1] and the number of trips is timed and gauged according to his charts for age, weight, and sex. The only difference from Master's technique is that an electrocardiogram with standard leads 1 and 2 and unipolar chest leads V_2, V_4, and V_5 is taken immediately after exercise. There are no repeat electrocardiograms after time intervals. The results of the exercise tests have been divided and analyzed according to the following responses:

1. In the ischemic type of response, the S-T segment is depressed 0.5 mm. or more below the P-R or P-Q junction in such a fashion that it subtends an angle of 90 degrees or more with the vertical (see figure, *left*). Therefore, the S-T segment is depressed in a horizontal or sagging course as described by Myers and Talmers.[2] This differs from the progressive concave ascent of the S-T segment in junctional depression (see figure, *right*).

2. In junctional changes the S-T segment ascends progressively in a concave fashion. An attempt was made to separate the true junctional changes



***Left*, types of ischemic depression. All are at least 90 degrees from vertical and 0.5 mm. below P-R junction. *Right*, types of junctional depression. All are less than 90 degrees from vertical. First two are true junctional depressions. Last is false depression due to tachycardia.**

from the false depression of tachycardia where the auricular T wave is exaggerated and continues after termination of the QRS interval (see figure, *right*). In the first group of junctional changes the S-T segment was depressed at least 1.5 mm. below the P-R junction.

3. In the second group of junctional changes, the S-T segment depression was at least 0.5 mm. but under 1.5 mm.

4. T-wave changes included flat, diphasic, inverted T waves, or upright T waves in one or more leads, after exercise, that were previously flat.

5. The arrhythmias included frequent premature auricular and premature ventricular contractions, bundle-branch block, and one case of paroxysmal tachycardia after exercise.

6. In the patients with abnormal resting electrocardiograms that showed changes after exercise, most of the resting electrocardiograms showed flat, diphasic, or shallow inversion of T waves in several leads. Some showed bundle-branch blocks. The changes after exercise included the five changes mentioned above. Many of these showed T waves that became upright after exercise but which were isoelectric in the resting electrocardiogram.

Analysis of Results

The total number of patients who were given double Master exercise tests from July, 1948, to March, 1955, and were followed three years or more after the first examination was 756. Of this number, a total of 280 had positive responses, using Master's original criteria [3] of any S-T depression of 0.5 mm. or over, upright, flat, or inverted T-wave changes, arrhythmias, and conduction defects or heart block after exercise. Although this is a high number, it will be seen in the subsequent analyses that this total number means very little. For the total 280 patients with positive test results, the age range was from 32 to 69 years, with a mean age of 53. Of these, 32, or 11.4%, developed classic angina pectoris, coronary insufficiency, or definite myocardial infarction within the 3-to-10-year follow-up. Again, in view of the subsequent analyses, this percentage has little meaning in itself.

There were a total of 476 patients who had negative exercise test results and were followed for the 3-to-10-year period. They had an age range of 23 to 74 years, with a mean age of 49. Of this group, 20, or 4.2%, developed classic angina pectoris, coronary insufficiency, or definite myocardial infarction.

Ischemic Responses.—In a total of 23 of the 280 positive Master tests the patients had typical ischemic responses. The age range of these patients was 36 to 63 years, with a mean age of 54. Six patients subsequently developed myocardial infarction, and 10 developed classic angina pectoris, so a total of 69.5% developed definite coronary disease.

Seven patients remained asymptomatic, and of this group five subsequently developed abnormal resting electrocardiograms, four of which showed abnormal nonspecific T-wave changes and one change compatible with left ventricular hypertrophy. Two of these seven patients continued to have normal resting electrocardiograms; one continued to show ischemic depression on the double Master exercise test but showed normal results after a single test, and the other showed a change from ischemic depression after exercise to a 1.5-mm. junctional depression after exercise. The latter patient was obese and in the interim lost approximately 30 lb. (13.6 kg.).

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Junctional S-T Segment Depression of 1.5 Mm. or Over.—A total of 23 patients in the group showed junctional S-T segment depression of 1.5 mm. or over; their ages ranged from 35 to 52 years, with a mean age of 50. Three patients subsequently developed myocardial infarctions; one died. Two patients subsequently developed classic angina pectoris. Therefore, a total of 21.7% developed definite coronary disease in this group.

Of the other 18 patients, 7 showed no change with a continuing junctional S-T segment depression of 1.5 mm. or over after exercise. Five subsequently had a negative Master exercise test result. Three subsequently had abnormal resting electrocardiograms, consisting of abnormal T waves of nonspecific patterns. For two patients the exercise test results changed to show lesser degrees of junctional depression (under 1.5 mm.), and in one the results remained unchanged after a double Master exercise test, but a single test showed negative results.

Junctional S-T Depression Between 0.5 and 1.5 Mm.—A total of 161 patients, with an age range of 30 to 67 years and a mean age of 50, showed junctional S-T depression between 0.5 and 1.5 mm. Of this group, four subsequently developed classic angina pectoris and there were no subsequent infarctions in the follow-up period, giving a total of 2.5% who developed coronary disease.

Of the remaining patients, 79 had negative Master exercise test results subsequently, 62 remained unchanged, 7 developed abnormal resting electrocardiograms (nonspecific abnormal T-waves changes), 5 developed junctional depression over 1.5 mm. in depth, and 4 subsequently developed ischemic depression after exercise.

Arrhythmias.—A total of 24 patients, with an age range of 32 to 66 years and a mean age of 51, developed arrhythmias. Three patients subsequently developed classic angina pectoris, of these, one had bigeminal premature ventricular contractions, one had transient right bundle-branch block, and one had transient left bundle-branch block after exercise; none developed subsequent myocardial infarctions, giving a total of 12.5% who developed coronary disease.

Among the other patients, there were 11 who developed premature ventricular contractions after exercise; for 7 of these the results subsequently became negative and in 4 remained unchanged. Nine patients developed premature auricular contractions after exercise; six of these subsequently showed negative results of exercise tests. In two patients, the results of the test remained unchanged, and one developed junctional depression of less than 1.5 mm. One patient developed transient auricular paroxysmal tachycardia in one lead after exercise, and in the following years the results of the tests became negative.

T-Wave Changes Only.—There were a total of 27 patients who showed T-wave changes only; their age range was 38 to 67 years, with a mean age of 54. Most of the T-wave changes included significant reduction of amplitude in one or more leads after exercise. Generally, the T waves became flat-diphasic or flat or developed shallow inversion in two or more leads. In only one case was there inversion of over 4 mm. in leads V_4 to V_6; this was in the only patient who developed classic angina pectoris, so only 3.6% of this group developed definite coronary disease.

Of the other patients, 12 subsequently showed negative exercise test results; 6 showed permanent abnormal resting electrocardiograms, five of which showed nonspecific T-wave changes and one a left bundle-branch block. In five patients, the exercise test result remained unchanged in the follow-up period. Two patients subsequently developed junctional depression under 1.5 mm., and one patient developed junctional depression of 1.5 mm. or more.

Abnormal Resting Electrocardiograms for Patients Showing Positive Responses After Exercise.—A total of 22 patients had abnormal resting electrocardiograms and positive results after exercise. Their ages ranged from 41 to 66 years, with a mean age of 55. Two patients subsequently developed myocardial infarction; both died. In both of these, the resting tracing showed nonspecific abnormal T-wave changes. After exercise one showed ischemic depression; the other showed upright T waves after exercise when they had been previously flat. Another patient subsequently developed angina pectoris. In this patient the resting tracing showed shallow inversion of T waves that became more inverted after exercise. This makes a total of 13.6% who developed coronary disease.

Of the other patients, 12 had abnormally flat T waves and developed upright T waves in one or more leads after exercise. Nine remained unchanged in the follow-up period of three or more years, and in three cases the results of exercise tests subsequently returned to normal. Three patients with nonspecific T-wave changes developed junctional depression of at least 1.5 mm. after exercise, and this remained unchanged in the follow-up period. Two patients had resting electrocardiograms compatible with left ventricular hypertrophy and strain and ischemic changes developed after exercise; these remained unchanged in the follow-up period. Two patients had right bundle-branch block. One of these developed ischemic changes after exercise, and one developed inverted T waves in the left chest lead after exercise. Both of these remained unchanged in the follow-up period.

Comment

It is evident from this analysis that the ischemic type of response had definite significance. In this group, 69.5% of the patients subsequently devel-

oped definite coronary disease in the 3-to-10-year follow-up period. It is worthwhile to compare this figure with that of clinically selected patients with known coronary disease. One of the largest groups is that of Russek,[4] who analyzed 186 patients with known coronary disease; 61.3% developed an ischemic type of response after a double Master exercise test. On the other hand, when Russek exercised 108 known healthy patients, 19.4% had positive Master test results according to Master's total criteria, but none of these had ischemic S-T segment depression. Robb and associates[5] gave double Master exercise tests to 69 patients with known coronary disease; 50.7% had ischemic changes. Although these figures are on clinically selected patients with known coronary disease, they are similar to those for the clinically unselected patients who were followed for 3 to 10 years for this report.

In analyzing the junctional changes over 1.5 mm., it cannot be dogmatically stated that these changes are significant, but it is probably more than chance that 21.7% did develop coronary disease. This is not in disagreement with Myers and Talmers,[2] who stated that if junctional depression is deep enough and not due to tachycardia it can be due to subendocardial ischemia.

In this study, it is evident that junctional changes under 1.5 mm. had no significance. Only 2.5% of the patients subsequently developed coronary disease, as compared to the control group, who showed negative results of the tests and of whom 4.2% developed coronary disease. Obviously, this group had no more coronary disease than the group with negative exercise tests. Four of these patients did subsequently develop ischemic depression after exercise, which according to this study has a poor prognosis, but even if this group is added to the number who developed coronary disease, it makes a total of only 5%, which is still not significantly different from the control group. These results are very different from Master's statements that any depression 0.5 mm. or over has definite significance.[1] There is only partial agreement with the work of Robb and associates.[5] They showed that the patients with ischemic response had an incidence of coronary occlusion of 79 per 1,000, while those with junctional response had a considerably lower incidence (35 per 1,000) but yet a significantly higher incidence than the group of those with negative test responses, who had an incidence of coronary occlusion of 9 per 1,000. However, they did not separate the junctional responses by degree but tabulated all junctional depression of 0.5 mm. or over in one group.

In the group with arrhythmias, the patients who developed coronary disease had transient bundle-branch blocks or bigeminal premature ventricular contractions after exercise. Since there were only three such cases, little can be said from this. However, it is evident that premature ventricular contractions and premature auricular contractions of no definite pattern had no significance.

The only patient who developed coronary disease in the T-wave change group had T-wave inversion of 4 mm. in leads V_4 to V_6. There was no correlation between development of subsequent coronary disease and minor T-wave changes.

Since an abnormal resting electrocardiogram may affect the patient's prognosis, it is difficult to say how significant the changes were that occurred in this group. It is interesting to note that two patients who had ischemic changes after exercise and who did not subsequently develop coronary disease had patterns of left ventricular hypertrophy and strain, which classically show an ischemic type of depression in the resting electrocardiogram.

Summary and Conclusions

Double Master two-step exercise tests were given to a group of 756 clinically unselected male patients who were followed for periods of 3 to 10 years. Ischemic changes after exercise, wherein the S-T segment is depressed horizontally or downward at least 90 degrees from the vertical and 0.5 mm. or more below the P-R or P-Q junction, had definite significance in diagnosis of potential clinical coronary disease. True junctional S-T segment depression over 1.5 mm. in depth, not due to tachycardia, was suggestive of potential coronary disease. On the other hand, there was no correlation between development of coronary disease and junctional S-T segment depression under 1.5 mm. in depth, minor T-wave changes, or minor transient arrhythmias such as premature auricular or premature ventricular contractions without a definite pattern.

Miss Dreama Morgan assisted in gathering data for this report, and Mr. Howard Southern drew the electrocardiograms.

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PROPHYLACTIC ANTIBIOTIC THERAPY IN INFANTS BORN AFTER PREMATURE RUPTURE OF MEMBRANES

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The death rate among infants born after premature rupture of the fetal membranes in a hospital rose sharply from 29 per 1,000 in 1954 to 144 per 1,000 in 1958. Various factors known to affect neonatal mortality in other situations were eliminated by analysis of the data until it appeared that the rise in death rate had followed the institution of a program of prophylaxis with antibiotics. Among 160 newborn infants who received such prophylaxis from January to May, 1958, 7 deaths occurred among 97 who received chloramphenicol with erythromycin, 5 among 8 who received chloramphenicol, erythromycin, and penicillin, and 5 among 5 infants who received chloramphenicol, erythromycin, penicillin, and streptomycin. Among the infants who died the characteristic syndrome included anorexia, lethargy, respiratory distress, a shock-like state, and a dusky gray appearance. The data were not sufficient to identify a single antibiotic as the sole cause, but no further cases of "gray sickness" occurred after the use of chloramphenicol was discontinued.

The neonatal death rate is usually slightly higher at University Hospital than at other hospitals in Jefferson County, probably because of a higher percentage of indigent patients, but during the last six months of 1957 and the first six months of 1958 this death rate rose significantly (fig. 1). The neonatal death rate of all the other hospitals in Jefferson County was relatively constant during this period. As there was no obvious cause, such as a nursery epidemic, for this rise in neonatal mortality, it was decided to evaluate the effectiveness of prophylactic administration of antibiotics in newborn infants during the period. Prophylactic antibiotic therapy had been used in the University Hospital to a limited extent for several years. During the last half of 1957 and the first part of 1958 three categories of indigent patients received prophylactic therapy: certain premature infants, infants born after unsterile delivery, and infants born after premature rupture of the maternal membranes. The last-named two groups routinely received some type of prophylactic antibiotic therapy. The largest group consisted of those born after premature rupture of the membranes, and for this reason it was selected for study.

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Materials and Method

The charts of all patients who delivered at the University Hospital during the first four months of 1954, a period when prophylactic antibiotic therapy in newborn infants was infrequently used, and for the first four months of 1958, a period when prophylactic antibiotic therapy was quite frequently used, were reviewed. The chart of each mother giving birth to a living child after premature rupture of the membranes was set aside and matched with her infant's chart. The following data were recorded from each mother's chart: age, race, diseases, obstetric complications, type of delivery, antibiotics received before delivery, length of rupture of the membranes, whether the membranes ruptured spontaneously or artificially, and number of prenatal clinic visits made. The birth weight, sex, race, type of prophylactic therapy, if any, symptoms, obstetric injuries, age at death, and autopsy findings, if available, were recorded for each infant. Antibiotic therapy was considered prophylactic if started within six hours after birth and before the onset of any clinical signs of infection. Six hours was the criterion used on the pediatric service during the period under study for premature rupture of the membranes, so the same criterion was used in this study.

The neonatal deaths in both groups of patients, those from 1954 and those from 1958, were further checked through the vital statistics bureau of the Jefferson County Public Health Department, because the infants' stay in the hospital varied considerably (1 to 30 days), particularly for 1954, and was usually only a fraction of the 28-day neonatal period. Several neonatal deaths in both 1954 and 1958 were found in this way.

Results

Data for both private and indigent patients were studied, but the results to be presented include only those from indigent patients (table 1). A comparison of indigent patients who did not receive prophylactic therapy with those who did is more valid than a similar comparison with private pa-

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tients, because the private patients during 1958 did not routinely receive prophylactic therapy with antibiotics.

The death rate in the 148 infants born after premature rupture of the maternal membranes in 1954 who did not receive prophylactic therapy was 29

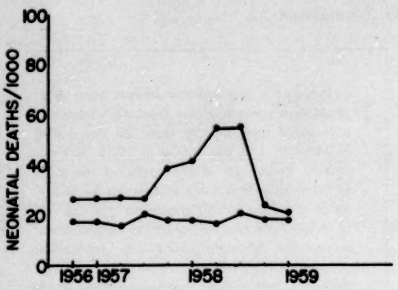

Fig. 1.—Neonatal death rates for University Hospital (*closed dots*) and all other hospitals in Jefferson County (*open dots*) for 1956, 1957, and 1958.

per 1,000 (table 2). When compared to the over-all neonatal death rate among indigent patients for the same period, 26 per 1,000, little difference is noted. This suggests that premature rupture of the membranes, at least in this group, did not appreciably affect mortality.

The neonatal death rate in the group receiving prophylactic therapy in 1958 was 144 per 1,000. This is almost five times the death rate of the group in 1954 that did not receive prophylactic therapy. The over-all neonatal death rate in indigent patients during the first four months of 1958 was 69 per 1,000 or slightly less than half the rate in the group receiving prophylactic therapy.

The difference in the death rates of the prophylactically treated and nontreated groups are statistically significant ($p<0.002$). The obvious difference

TABLE 1.—*Premature Rupture of Membranes in Indigent Patients*

	Jan.-May, 1954	Jan.-May, 1958
Total births	988	1,070
Births after premature rupture of the membranes	148	179
Patients receiving prophylactic antibiotic therapy	11	160
Patients with premature rupture but no prophylactic antibiotic therapy	137	19

in the two groups was the use of antibiotics. Other factors known to affect neonatal mortality have been studied (table 3). The incidence of prematurity in the two groups was the same. The fact that almost half of those who died after prophylactic therapy were full-term infants further indicates that prematurity does not explain the rise in neonatal mortality (table 4). The relative incidences of prolonged rupture of the membranes (24 hours or more) was not significantly different. The racial composition of the two groups was also similar (table 3). The latter is of importance, as neonatal mortality is higher among Negroes in this area. No other obvious difference between the prophylac-

TABLE 2.—*Neonatal Death on Indigent Service*

	Jan.-May, 1954		Jan.-May, 1958	
	No.	Per 1,000	No.	Per 1,000
Total live births	988		1,070	
Total deaths	24	26	74	69
Premature rupture with no prophylactic therapy	148	...	...	...
Premature rupture with prophylactic therapy	...	...	160	...
Deaths with no prophylactic therapy	4	29	...	...
Deaths with prophylactic therapy	...	...	23	144

tically treated and the nontreated groups, such as age, parity, prenatal clinic visits, or maternal disease, was noted.

In addition to the 23 patients in the group given prophylactic treatment with antibiotics who died were 8 other infants who showed a characteristic clinical syndrome but did not die. Of the 23 infants who died 14 showed a similar clinical picture. These infants appeared normal until the second to fifth day after birth (table 4). They then typically stopped eating and became hypoactive and lethargic. Respiratory distress with rapid, shallow, irregular respirations was quite common. The dusky gray appearance of these infants was so characteristic that the pediatric residents working in the nursery at the time referred to the syndrome as the "gray sickness." The appearance of these infants suggested to several observers that the infants were in shock. Most of them presented a clinical picture of gram-negative septicemia. Blood cultures during life and culture of the lungs in those who came to autopsy were done routinely but no positive cul-

TABLE 3.—*Prophylactically Treated Group (1958) Versus Nontreated Group (1954)*

		No.	%
1954*	Negroes	103	77
1958†	Negroes	128	80
1954	Membranes ruptured for 24 hr. or more	53	39
1958	Membranes ruptured for 24 hr. or more	57	36
1954	Premature births	24	18
1958	Premature births	28	18

* Total patients=137.
† Total patients=160.

tures were found in the 14 infants with the above symptoms. Virus studies of blood and lungs obtained at autopsy also failed to reveal pathogens.

Comment

Prophylactic antibiotic therapy has been tried in a number of situations in medicine and has been proved valuable in very few. Prophylactic treatment with penicillin has been shown to decrease

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the rate of recurrence in patients who have had rheumatic fever.[1] The patients were being protected against a single organism whose sensitivity was known. The use of prophylactic antibiotics to protect surgical patients, children with measles or upper respiratory infections, and unconscious patients from secondary bacterial infection has not been successful.[2] In these situations the patients must be protected from a variety of organisms with unknown sensitivities. Prophylactic use of antistrains of bacteria in the nursery. Finally, one or more of the antibiotics used may be toxic to the newborn infant. Newborn infants may not be prepared as well metabolically as are adults to tolerate one or more of the antibiotics used. If either of the first two factors were operating one would have expected to see evidence of infection in infants coming to autopsy. The demonstration of infection in the infant autopsies during this period was infrequent. Evaluation of toxicity of the antibiotics

TABLE 4.—*Analysis of Twenty-three Deaths in Prophylactically Treated Group*

Case	Race, Sex	Birth Weight, Gm.	Length of Rupture of Membranes, Hr.	Age at Onset of Symptoms, Days	Antibiotics Administered*	Age at Death, Days	Findings at Autopsy
1	N, M	2,500	24	2	Chloramphenicol, erythromycin	2	Lobular pneumonia, slight†
2	N, M	2,020	56	0	Chloramphenicol	2	None
3	N, M	2,460	8	5	Chloramphenicol, erythromycin	5	None
4	N, M	3,912	26	4	Chloramphenicol, penicillin	4	None
5	N, M	2,722	8	5	Chloramphenicol	5	None
6	N, M	1,417	7 days	4	Chloramphenicol, erythromycin	4	None
7	N, M	3,083	6	5	Chloramphenicol, erythromycin	5	Atelectasis, minimal†; fatty change in liver
8	N, M	2,728	48	3	Chloramphenicol, erythromycin, penicillin	4	None
9	N, M	2,892	12	5	Chloramphenicol, erythromycin-neomycin, penicillin	5	Yes†
10	N, M	2,420	12	5	Chloramphenicol	8	Bronchial pneumonia, bilateral
11	N, M	3,065	6½	3	Chloramphenicol penicillin, neomycin, streptomycin	20	None
12	N, F	2,750	22	6	Chloramphenicol, penicillin, streptomycin, novobiocin, neomycin	16	Yes†
13	C, M	1,817	6	5	Chloramphenicol, erythromycin, penicillin	6	Yes†
14	C, M	2,098	60	4	Chloramphenicol, erythromycin, penicillin	6	Yes†
15	C, F	1,440	7 days	0	Chloramphenicol, penicillin, streptomycin	6½ hr.	None
16	C, F	1,966	7 days	3	Chloramphenicol, erythromycin, penicillin	6	None
17	C, M	1,899	19	2	Chloramphenicol, penicillin	2	Atelectasis, slight,† petechial hemorrhages in lungs
18	N, M	1,916	43	5	Chloramphenicol, erythromycin, penicillin	6	None
19	C, F	3,062	17	2	Chloramphenicol, erythromycin, penicillin	2	None
20	N, M	2,540	17	3	Chloramphenicol, erythromycin	4	Truncus arteriosus
21	N, F	2,260	4½ days	3	Chloramphenicol, penicillin, streptomycin, neomycin, novobiocin	4	None
22	N, F	1,871	39	4	Chloramphenicol, penicillin, streptomycin	5	None
23	N, F	2,700	6	5	Chloramphenicol	5	Petechial hemorrhages in lungs and stomach†

* Prophylactic antibiotics were administered within six hours of birth and were continued for five to seven days. The dosages used varied: chloramphenicol (Chloromycetin), 50 to 100 mg. every 8 or 12 hr.; erythromycin (Ilotycin), 50 mg. every 8 hr.; penicillin, 50,000 to 150,000 units every 12 hr.; streptomycin, 30 to 125 mg. every 12 hr.; neomycin, 10 to 15 mg. every 8 or 12 hr.; and novobiocin, 50 mg. every 8 to 12 hr.
† No anatomic lesion noted or no adequate explanation for symptoms and death.

biotics after premature rupture of the membranes was more in common with the latter use, since the vaginal flora are quite varied.

In considering ways that prophylactic antibiotic therapy in the newborn infant may contribute to an increase in mortality, three possibilities come to mind. First, some of the antibiotics were given by injection, which provides an additional portal of entry for bacteria. Second, extensive use of antibiotics may result in the development of resistant

used is complicated because combinations of antibiotics were usually employed (table 5). Four antibiotics in eight different combinations were used in the prophylactic program. Also, additional antibiotics were added to the treatment schedules of some infants during the course of their illness. However, chloramphenicol was the drug most extensively used; 145 of the 160 infants who had prophylactic therapy received chloramphenicol. Furthermore, all of the infants who died, as well

as the eight with the "gray sickness" who lived, received chloramphenicol in doses ranging from 100 to 300 mg. every 24 hours. Erythromycin was the next most commonly used drug. It was given only with chloramphenicol. There were several infants who died and others who had the "gray sickness" who did not receive erythromycin. Further correlation between the increase in the use of chloramphenicol in the nursery and the neonatal death rate is striking (fig. 2). The relative frequency of the use of chloramphenicol in the program of prophylactic therapy was determined by reviewing 20 or 25 charts, selected at random by the record room, of infants receiving prophylactic therapy for each month during 1957 and 1958.

TABLE 5.—*Antibiotic Combinations Administered in 160 Newborn Infants January-May, 1958*

Antibiotics Received	No. of Patients	Deaths
Chloramphenicol	5	1
Chloramphenicol and erythromycin	97	7
Chloramphenicol, erythromycin, and penicillin	8	5
Chloramphenicol, erythromycin, penicillin, and neomycin*	1	1
Chloramphenicol, erythromycin, and neomycin*	2	1
Chloramphenicol, erythromycin, neomycin, and novobiocin*	2	1
Chloramphenicol and penicillin	4	2
Chloramphenicol, penicillin, and streptomycin	11	2
Chloramphenicol, penicillin, streptomycin and neomycin*	1	1
Chloramphenicol, penicillin, streptomycin, neomycin, and novobiocin*	1	1
Chloramphenicol, penicillin, streptomycin, neomycin and novobiocin	3	1
Chloramphenicol, erythromycin, penicillin, and streptomycin	5	5
Penicillin and streptomycin	12	...
Penicillin	1	...
Penicillin, streptomycin, and novobiocin*	1	...
Neomycin	1	...

* Except in one case neomycin and novobiocin were added late in the course of illness; that is, they were not used prophylactically.

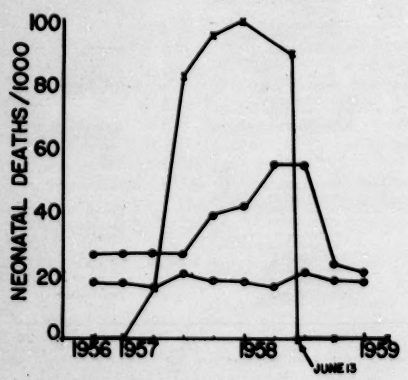

Fig. 2.—Neonatal death rates for University Hospital and all other hospitals in Jefferson County for 1956, 1957, and 1958, with percentage of group in University Hospital nursery receiving prophylactic therapy with chloramphenicol (*crosses*) added.

The rise in the neonatal death rate followed the increase in the use of chloramphenicol in the prophylactic program. When the use of chloramphenicol in the nursery was discontinued on June 13, 1958, the neonatal death rate dropped back to and remained at about the level present before the use of chloramphenicol. Several changes were made in the operation of the nursery during the spring of 1958, in an attempt to lower the neonatal death rate, which makes this portion of the two curves shown in figure 2 more difficult to evaluate. However, there was no notable change in the operation of the nursery in July, 1957, when the rate began to rise, other than the increased use of prophylactic therapy with antibiotics and the change from penicillin and streptomycin to chloramphenicol and erythromycin as the recommended drugs. Furthermore, the "gray sickness" has disappeared from the nursery since use of chloramphenicol was discontinued on June 13, 1958.

TABLE 6.—*Antibiotic Therapy in Infants Born to Indigent Patients in March, 1958*

	Patients, No.	Deaths	
		No.	per 1,000
Total deliveries	297	25	84
No antibiotic therapy	205	4	20
Total receiving antibiotic therapy	92	21	228
Chloramphenicol therapy	84	19	226
Prophylactic antibiotic therapy	79	16	202

The role that prophylactic antibiotic therapy may have played in the over-all increase in neonatal mortality is of interest. When the over-all neonatal death rate of the first four months of 1954, 26 per 1,000, and 1958, 69 per 1,000, are compared, it should be kept in mind that the latter includes the group of those born after premature rupture of the maternal membranes and given prophylactic therapy, with its high mortality. If this group is simply removed from the total, the over-all rate drops to 56 per 1,000. It also includes two other groups of infants given prophylactic therapy; infants having nonsterile deliveries and certain premature infants. To gain some insight into the over-all frequency of prophylactic therapy during the first four months of 1958, the charts of all the infants born in March, 1958, were reviewed (table 6). It is evident that almost one-third of the infants born in this period received antibiotic therapy. In most instances this was prophylactic therapy which usually included chloramphenicol. Furthermore, 19 of the 25 infants dying during this month received chloramphenicol. These data suggest that if chloramphenicol therapy is not well tolerated by newborn infants, its use was extensive enough during this period for it to have been a major factor in the over-all rise in neonatal death rate at the University Hospital.

Summary

The neonatal death rate in a group of 148 infants born after premature rupture of the maternal membranes who received no prophylactic antibiotic therapy was determined and compared to that of a similar group of 160 infants who did receive such therapy. The death rate in the latter group was 144 per 1,000, as compared to 29 per 1,000 in the former. There is a possibility that the increase in neonatal mortality was due to chloramphenicol toxicity, but the evidence presented does not prove a relationship between the increased death rate in the infants receiving prophylactic therapy and chloramphenicol therapy; however, it is sufficient to suggest the need for some evaluation of the toxicity of chloramphenicol in the newborn infant.

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The bacterial culture and virus studies were performed by Drs. Charles Winkler and Robert Francis, Department of Microbiology, respectively. Dr. Sara Finley, Department of Pediatrics, supplied important data.

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CLINICAL NOTES

ISOSENSITIZATION TO THE U FACTOR

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Reported instances of sensitization to the U factor are extremely rare; in fact, we could find only three cases reported in the literature. In 1953 Wiener and co-workers [1] reported a fatal hemolytic transfusion reaction caused by sensitization to a previously unreported blood factor which they designated as U. Greenwalt and co-workers,[2] in 1954, and Wiener and Unger,[3] in 1958, reported the second and third cases respectively. All of these cases occurred in Negroes. We believe that the case presented here represents the fourth reported instance of isosensitization to the U factor.

Report of a Case

A 58-year-old Negro man was admitted to Freedmen's Hospital on March 19, 1959, for treatment of a malignancy of the prostate gland. On admission, a blood count showed 8.3 Gm. of hemoglobin per 100 cc., 27% hematocrit, and 11,000 white blood cells per cubic millimeter, with 66% neutrophils, 27% lymphocytes, and 5% eosinophils. The patient denied having received previous blood transfusions. Two pints of blood was requested to help correct the anemia. Initial blood bank studies showed that the patient's blood was group O, type Rh_0 (cDe). Both donors were of similar type. Routine crossmatches, performed in saline solution, albumin, and antihuman globulin, were compatible and on March 20, 1959, 1,000 cc. of blood was given, with no noticeable reaction. Nine days after the transfusions more blood was requested. At this time, however, there was agglutination on the major side of the albumin crossmatch with numerous specimens of blood belonging to the patient's blood group. The saline and antihuman globulin determinations were compatible. Results of the indirect Coombs test and tests for cold and warm agglutinins were negative. Several attempts to secure compatible blood during the next few weeks failed. Four weeks after transfusion the result of the indirect Coombs test became positive with a titer of 1:128, and the albumin titer was 1:16. Agglutination was still negative in saline solution. Since these determinations showed presence of a blocking antibody, tests for the **M, N, P, Duffy, Cellano,** and **Kell** factors were performed. Since results of these, all being positive, were not revealing, a specimen of the patient's blood was sent to the National Institutes of Health, Bethesda, Md., for further testing. Here it was shown that the patient was U-negative and had antibodies to this factor. Subsequent testing showed that the donors were U-positive. Attempts were then made to secure U-nega-

From the blood bank of Freedmen's Hospital and Department of Pathology, Howard University, College of Medicine.

tive blood but all were unsuccessful. Two months after hospitalization and surgery the patient showed improvement, and plans were made for his discharge.

Comment

The U factor is almost universally present in human erythrocytes. Studies by Wiener and co-workers [4] showed that every blood specimen from a series of 1,100 Caucasians contained the U factor, whereas among those from 989 Negroes 12 did not have the U factor. Further studies showed that this factor is not related to the A-B-O, Rh-Hr, Duffy, Kidd, Lutheran, Lewis, or P blood-group systems. It was noted, however, that all 12 U-negative persons had blood of type N or MN, which suggested a possible relationship to this system. Sanger and co-workers [5] noted that all U-negative persons lacked the S and s factors which belong to the MNS system. This finding proved that the U factor is a part of the MNS system. Wiener and co-workers [1] reported that the U factor is inherited as a simple mendelian dominant.

This case is similar to those previously reported in that the patient was Negro and had type MN blood. There was no apparent relationship to other blood-group systems. The antibody found was of the univalent or blocking type, as was noted in the case of Greenwalt and co-workers [2] and in the second case of Wiener and Unger.[3]

It is of interest to note that 1.2% of Negroes tested are U-negative. Because of this fact, many problems are readily apparent. Hospitals treating Negro patients should be charged with the responsibility for proper selection of blood donors to prevent immunization to the U factor. Sensitization to this factor in U-negative Negro women with U-positive husbands may be a cause of erythroblastosis fetalis in their babies. Fatal hemolytic transfusion reactions may occur, as noted in the case reported by Wiener and co-workers.[1] Since agglutination was observed in our case on a routine albumin crossmatch, the possibility of a fatal hemolytic reaction was averted. Once these persons are sensitized, they must receive U-negative blood only, and this presents a problem, due to the scarcity of U-negative donors. Since blood banks do not routinely test for this factor, it behooves every clinician treating Negro patients to be discerning and judicious in ordering blood transfusions.

Help in identifying the antibody and confirmation of earlier findings were given by Dr. John S. Fordtran of the National Institutes of Health.

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CONTINENTAL BREAKFASTS FOR HOSPITAL PATIENTS.—Like most hospitals, St. Luke's [in Jacksonville, Fla.] was faced with the problem of awakening the patient early for baths and medications, and then keeping him happy until the breakfast service started at 8 a.m. W. E. Arnold, executive director of the 210-bed hospital, worried about the problem until a chance business meeting in New York gave him the solution. An early riser, Mr. Arnold was delighted to find an insulated container of hot coffee and a hard roll with butter and jelly deposited at daybreak in the service slot of his hotel room. A comparable solution could be effected, he felt, in the hospital by young girls serving pots of hot coffee and buns to all patients who wanted an early snack. In the spring of 1954 final plans for a "continental breakfast cart" were put into operation. Two high school girls were employed . . . to come in at 5:30 in the morning to prepare the carts, one for each of the two floors. By 6 o'clock the girls were dressed in white pinafores over blue dresses and had the carts ready for service on the floors. Each cart is equipped with an insulated container of hot coffee, one of hot water for tea, a warmer filled with hard rolls and sweet rolls, butter and jelly. . . . A cup of steaming hot coffee and a roll are served to each patient who asks the night before to be put on the pre-breakfast list. Service is not made, of course, if chart orders conflict. . . . The average daily cost of this service is approximately 12 cents per person. "We feel that this is a small price to pay for a contented patient," Executive Director Arnold said. "The nurses and doctors find the patient more cooperative; the dietary department is well repaid for the extra effort by the enthusiastic reception the service receives."—Continental Breakfast Builds Good Will at Low Cost, *Hospitals*, May 16, 1959.

SPECIAL ARTICLE

PRIMER ON THE RHEUMATIC DISEASES

PART I

Prepared by a Committee of the American Rheumatism Association

This is the fifth edition of the Primer on the Rheumatic Diseases, previous editions having been published in 1934, 1942, 1949, and 1953. This publication presents basic material concerning rheumatic diseases in as simple and concise a form as is consistent with adequate coverage, bearing in mind the particular needs of the general physician and the student. The voluminous and rapidly expanding literature is not cited because of the condensed nature of the primer. The 12th "Review of American and English Literature," the previous "Reviews," and textbooks by outstanding authorities in the field are available in medical libraries for more extensive reading and background. The new journal *Arthritis and Rheumatism*, now the official organ of the American Rheumatism Association, and the *Annals of the Rheumatic Diseases*, published in London, provide the clinician with an abundant source of current articles on these subjects.

The terms "rheumatism" and "rheumatic diseases" are now accepted as synonymous and are used to indicate any painful disorder in which the principal symptoms are related to the joints or their anatomic supporting structures. Rheumatic fever; various types of degenerative, inflammatory, and metabolic arthritis; a large group of ill-defined conditions such as fibrositis, tendinitis, myositis, and neuritis; and the so-called collagen or connective tissue disorders are included in this category and are the chief concern of this primer. Certain other diseases which present secondary manifestations referred to articular structures are included more briefly for differential diagnostic purposes.

Incidence of Rheumatic Disease

A full-scale population sampling to discover the prevalence of various diseases and the influences of environmental factors has not been accomplished in the United States since 1937. This sorely needed study is contemplated for 1959.

Previous studies have revealed that articular and nonarticular rheumatic diseases, exclusive of rheumatic heart disease, disable almost 10% of the population, 10 times as many as diabetes, 7 times as many as cancer, and twice as many as heart disease. The results of all such surveys are, of course, open to criticism. Large population surveys, however well planned from the statistical and representative standpoints, lack diagnostic accuracy. Clinic, hospital, and private office surveys, on the other hand, provide more accurate diagnoses but may lack representative sampling. Despite this, any investigation indicates that the rheumatic diseases are a formidable group of illnesses, from the standpoint of the number of persons affected and the total disability engendered.

The Canadian sickness survey of 1950-1951 revealed that 225,000 persons, of the total population of 15 million, had arthritis or rheumatism. Of these 50,000 were severely or totally disabled solely or primarily because of rheumatic diseases. This incidence is considerably lower than estimates in this country, apparently because a large number of mild or nondisabling rheumatic disorders and rheumatic fever were not included.

Information gathered by lay interviewers in five U. S. Public Health Service surveys in 18 states over a 25-year period up to 1955 is summarized in table 1.

Other studies indicate that, of the 10 million persons in the United States thought to have some form of rheumatism, 4,500,000 have true arthritis, with 200,000 being totally disabled and 800,000 partially disabled. Lost wages approximate 700 million dollars annually. Rheumatic fever alone, while declining in mortality from 6 per 100,000 population in 1905 to 0.3 per 100,000 in 1953, still affected 1 million persons in the United States.

Figures from the Netherlands, with a population of 11 million, indicate that rheumatism affects 15% of males and 20% of females over 15 years of age. Of the 10,000 or more affected by rheumatoid arthritis, with or without spondylitis, at least 10% were incurable invalids. Twenty per cent of all sickness benefits issued in 1953 were for rheumatic diseases.

This is the first of three installments. The second will appear in the Nov. 7 issue.

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Reprints of the full text of this primer are available from the American Rheumatism Association, 10 Columbus Circle, New York 19. The price per copy is 50 cents.

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Organization of the Attack on Rheumatic Diseases

During the past quarter-century medical societies devoted to the study of rheumatic diseases have been organized in most of the principal countries of the world. Of these the American Rheumatism Association continues to be numerically the largest, with over 1,200 members. In addition to national societies, international boundaries are crossed in the Pan American League Against Rheumatism, the European League Against Rheumatism, and the International League Against Rheumatism. The American Rheumatism Society holds two meetings each year. Most of the other national societies meet once a year, and the International League meets once every four years. The interest in these meetings among rheumatologists as well as nonrheumatologists emphasizes the rising tide of energies in professional fields to find causes and cures for the rheumatic diseases.

TABLE 1.—*Incidence of Various Rheumatic Diseases—Effect on Disability and Hospitalization**

Rates per 1,000 Population, No.	Arthritis and Chronic Rheumatism	Rheumatic Fever	Other Diseases of Bones, Joints, and Locomotor Organs	Lumbago, Myalgia, and Myositis	Backache
Total cases	17.0	2.3	7.3	6.1	3.0
Disabled cases†	8.5	1.9	3.1	3.5	1.3
Bed cases‡	5.3	1.5	1.7	2.2	0.78
Days of disability per 1,000 population	934.0	255.5	194.0	26.1	...
Mean days of disability per case	180.5	125.1	75.3	8.3	...
Hospital admissions per 1,000 population	0.59	0.17	0.72	...	...
Hospital days per 1,000 population	4.8	36.7	40.2	...	...
Mean days per hospital admission	12.1	168.7	61.3	...	...
Mean hospital days per case	...	54.3	46.7	...	...

* All data calculated on basis of annual incidence.
† Unable to perform usual duties for one day or more.
‡ Confined to bed more than one day.

The establishment in the United States in 1951 of the National Institute of Arthritis and Metabolic Diseases as one of the National Institutes of Health allied the resources of our federal government with those of the voluntary organizations and other interested parties in a nationwide attack on this group of afflictions. Through the research conducted in its own laboratories at Bethesda, Md., and by means of grants to nonfederal institutions, the Institute has become a major partner in this effort in a relatively brief period. The research grants program provides financial support to qualified scientists throughout the country for a wide variety of fundamental laboratory research and applied investigations necessary to continued advances in the pathogenesis, diagnosis, and treatment of these diseases as well as rehabilitation of persons afflicted with arthritis. At the same time, the institute's training grants program has been a major factor contributing to effective dissemination of knowledge and modern concepts of rheumatic diseases among medical students and physicians. Grants supporting general training in rheumatology have been awarded to almost half of the nation's medical schools, and this number can be expected to increase as additional highly trained physicians become available for academic positions. A third program, for the advanced training of outstanding persons, provides stipends for one or more years of specialized activity.

Also assisting in the attack on rheumatic diseases is the Arthritis and Rheumatism Foundation, a voluntary fund-raising health agency whose medical program (research, professional education, and medical care) is formulated and implemented by a medical and scientific committee consisting of physicians and scientists nominated to office by the American Rheumatism Association. The foundation has 53 chapters in 41 states. Among its professional activities the foundation conducts a research fellowship program which awards annually about 30 predoctorate, postdoctorate, and five-year senior investigator fellowships. The foundation publishes the *Bulletin on Rheumatic Disease*, a monthly scientific publication, which it distributes to about 45,000 physicians in every continent of the globe. The "Primer on Rheumatic Diseases" is distributed by the foundation annually to senior medical students and the "Rheumatism Reviews" to interns, residents, and fellows. In addition, the several professional educational activities of the American Rheumatism Association are supported almost entirely by the Arthritis and Rheumatism Foundation.

Classification of Rheumatic Diseases

The classification of rheumatic diseases used herein is that which has been officially adopted by both the American Rheumatism Association and the Standard Nomenclature of Diseases and Operations.

There are, of course, inherent difficulties in classifying diseases whose etiology is unknown. For this reason, differences of opinion are held on several items in this table. For example, there is good evidence, both clinical and laboratory, that rheumatoid spondylitis differs in important respects from rheumatoid arthritis, while arthritis associated with psoriasis differs from the classic variety. Many clinicians feel that these differences should be more adequately expressed in the classification. In addition, some continue to prefer the simpler "osteoarthritis" to the more descriptive "degenerative joint disease." The term "mixed arthritis" is dropping out of usage and is not included here, even though some patients may manifest both rheumatoid and degenerative joint disease. The preferable custom of diagnosing the major cause of disability, with secondary diagnosis of less important condition, is customarily used. It is open to question whether "intermittent hydrarthrosis" deserves a

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separate heading, or whether "fibrositis" and "myositis" can be listed as individual entities; the painful shoulder syndromes warrant more precise designation. As clearer understanding of the various diseases is obtained changes will, of course, be made. However, the benefits of a standard classification and terminology outweigh minor differences of opinion regarding form.

Rheumatic Fever

Rheumatic fever is an inflammatory process of unknown etiology, characterized by acute polyarthritis, with accompanying carditis, which may become chronic. All ages are susceptible but the greatest incidence of the disease occurs in children between 6 and 9 years of age. In the United States a definite geographical pattern is discernible, with Colorado, Utah, New York, Pennsylvania, and Massachusetts reporting the highest proportion of cases. The exact incidence of the disease is difficult to determine, since the occurrence of late chronic manifestations without recognized antecedent acute episodes indicates the existence of symptomless or atypical forms not presently understood. In countries where rheumatic fever is reportable rates vary from 11 to 30 per 10,000 persons per year. Rheumatic heart disease has been found in 1 to 4% of school children, while 7% of serial autopsies at a general hospital showed evidence of such cardiac abnormalities. Acute attacks have shown a declining rate in recent years. Although this is in part due to the widespread use of antibiotics in the treatment of patients with upper respiratory disorders, other factors such as improved nutrition and housing are of apparent significance, since the decrease had been noted prior to the advent of specific antistreptococcic therapy.

Etiology.—The etiology of rheumatic fever remains an enigma. Although acute episodes characteristically develop 10 to 20 days after upper respiratory infections due to group A beta hemolytic streptococci, organisms cannot be recovered from involved tissues or body fluids other than the pharynx, and even these are frequently not obtained after the onset of symptoms. Specific antibacterial therapy is of prophylactic value but useless as a therapeutic measure. Hypersensitivity suggested by these data lacks significant supportive evidence, as do other hypotheses of etiology. It is therefore apparent that, although infection by the beta hemolytic streptococcus initiates the disease process, the exact mechanism by which this is accomplished is unknown.

Pathology.—The lesions of rheumatic fever may be found in many organs, but the heart is the site of the most characteristic and consequential involvement. All portions of the heart may be affected. The characteristic microscopic lesion, known as the Aschoff body, is a submiliary granuloma, usually located adjacent to small myocardial vessels; however, it may occur in other cardiac and extracardiac locations. Swelling and fragmentation of collagen fibers are found in these foci as well as aggregations of characteristic large cells; these lesions heal with scar formation. The Aschoff bodies are generally regarded as pathognomonic of rheumatic activity, and it is of considerable importance that they are found in approximately 40% of auricular appendages amputated during mitral commissurotomy in clinically quiescent cases of rheumatic heart disease. Verrucous valvulitis is followed by healing with fibrous thickening and adhesion of valve commissures and chordae tendineae. This leads to variable degrees of incompetence or stenosis of the valves and resultant hypertrophy and dilatation of the heart. Subcutaneous nodules, seen during active phases of the disease, are composed of edematous, cellular granulomatous tissue. The cells involved closely resemble those of the Aschoff body, and localized areas of "fibrinoid" swelling of subcutaneous collagen bundles may occur. Unlike the subcutaneous nodules of rheumatoid arthritis little necrosis or fibrosis is seen. Synovitis is usually mild and nonspecific; however, foci comparable to subcutaneous nodules may be seen within the wall of the joint. Disseminated arteritis occurs, particularly within the lungs. The status of rheumatic pneumonia remains controversial at present.

TABLE 2.—*Classification of Rheumatic Diseases*

Arthritis due to infection. Specify joint and infection, when known, as:
- Arthritis of the spine due to tuberculosis
- Arthritis of the knee due to gonococcic infection
- Arthritis of the wrist due to pneumococcic infection
- Arthritis of the knee due to syphilis

Arthritis due to rheumatic fever. Record rheumatic fever as primary diagnosis invariably

Arthritis, rheumatoid, of ... Specify, as:
- Arthritis, rheumatoid, multiple (proliferative arthritis, atrophic arthritis, chronic infectious arthritis, Still's disease*)
- Arthritis, rheumatoid, of spine (Marie-Strumpell arthritis, ankylosing spondylitis, von Bechterew spondylitis, spondylitis ankylopoietica, spondylitis rhizomelique)

Arthritis due to direct trauma of ... Specify joint and trauma, as:
- Arthritis of knee due to contusion
- Arthritis of elbow due to habitual dislocation

Neurogenic arthropathy (Charcot joint). Specify joint and cause, as:
- Tabetic arthropathy of knee

Arthritis due to gout. Specify joint. Record gout as primary diagnosis invariably

Degenerative joint disease, multiple, due to unknown cause (osteoarthritis, hypertrophic arthritis, degenerative arthritis, chronic senescent arthritis)

New growths of joints. Specify joint and neoplasm, as:
- Synovioma of knee

Hydrarthrosis, intermittent of ... Specify joint

Fibrositis. Specify joint or area

Myositis, bursitis, neuritis, and neuralgia. Specify muscle, bursa, or nerve involved

Diseases in which arthritis, arthropathy, or arthralgia is frequently associated (diagnose disease, list joint manifestation as symptom):
- Acromegaly
- Acute disseminated lupus erythematosus
- Cyst of meniscus of knee
- Dermatomyositis
- Drug intoxication. Specify drug when known
- Erythema multiforme exudativum
- Erythema nodosum
- Hemophilia
- Hysteria
- Ochronosis
- Osteochondritis dissecans
- Osteochondromatosis
- Polyarteritis nodosa
- Psoriasis
- Purpura, various types
- Raynaud's disease
- Scleroderma
- Serum sickness

* Names in parentheses are synonyms.

Clinical Features.—The classic attack of rheumatic fever appears as an acute migratory polyarthritis involving primarily the larger joints and accompanied by signs and symptoms of an acute febrile illness. In approximately one-half of the cases it is possible to elicit a history of a preceding upper respiratory infection, with an intervening latent asymptomatic period of one to three weeks' duration.

Evidence of cardiac involvement may be noted concurrent with the first arthritic symptoms or may appear shortly thereafter. These may include signs of myocarditis, pericarditis, or valvular disease (usually the mitral, less commonly the aortic valve, or involving both the mitral and the aortic), a prolonged P-R interval in the electrocardiogram, and congestive heart failure. Various skin rashes, particularly erythema marginatum, are not uncommon; subcutaneous nodules are a less frequent finding. Pleuritic, precordial, or abdominal pain may occur, with mild or absent joint symptoms, making the diagnosis difficult. Evidences of constitutional involvement include headache, lassitude, fatigue, fever, anorexia, and nausea; prostration may be present in severe cases. Patients with rheumatic heart disease may develop subacute bacterial endocarditis. Chorea minor (Sydenham's chorea) is frequently associated with juvenile rheumatic fever and may be causally related to it.

The course of the disease is subject to extreme variations. Patients with mild cases may have only a transient polyarthritis of a few days' duration; those with severe cases may run the gamut of all signs and symptoms noted above, progressing to severe toxemia, cardiac decompensation, and death within several weeks. With treatment, however, the majority will make a complete recovery within three to four months. But recurrences, in the absence of streptococcic prophylaxis, are not rare, and with each attack the possibility of permanent heart damage is increased. It has been well stated that rheumatic fever "licks the joints but bites the heart."

Laboratory Findings.—Although no specific test will establish the diagnosis, certain laboratory findings are extremely helpful. Chief among these are changes in the electrocardiogram (primarily prolongation of the P-R interval above 0.18 in children and 0.21 seconds in adults) and elevation of the serum antistreptolysin-0 titer (above 200 in most laboratories, although standards vary). Anemia, leukocytosis, elevated sedimentation rate, and positive C-reactive protein test result are also noted during the acute phase of the disease. Group A hemolytic streptococci may at times be recovered from the pharynx in the early stages. As the disease continues pharyngeal cultures and those from other tissues and fluids are negative.

Differential Diagnosis.—Early cases of rheumatic fever may at times be confused with rheumatoid arthritis and differentiated only by adequate observation of the course of the disease over several weeks or months. Historical or serologic evidence of a preceding streptococcic throat infection suggests rheumatic fever, as does a change in the electrocardiogram. In general, the patient with acute rheumatic fever appears sicker, has a higher temperature, a greater leukocytosis, and a more dramatic response to treatment with salicylates than does the patient with rheumatoid arthritis presenting comparable joint involvement. As time goes on the arthritis subsides, leaving no residual articular damage, whereas the heart may show permanent injury. In rheumatoid arthritis, however, the opposite is the rule and the joint involvement becomes more persistent. Laboratory aids may be helpful in differentiation: In rheumatic fever the antistreptolysin titer is elevated and the agglutination titer for sensitized sheep cells and latex or bentonite particles is normal. Congenital heart disease or tuberculous pericarditis occasionally presents facets clinically compatible with rheumatic fever, but consideration of the total picture, including duration, severity, and the presence or absence of other lesions, usually aids in establishing the correct diagnosis. Fever of undetermined origin may be rheumatic. If a patient is known to have had prior rheumatic valvular disease, repeated blood cultures may be indicated, since subacute bacterial endocarditis is a possible cause of fever in a person known to be rheumatic. A picture similar to that of rheumatic fever may be presented by a group of systemic inflammatory diseases affecting similar structures in the body; these include polyarteritis nodosa, systemic lupus erythematosus, and dermatomyositis. These are rare enough to warrant preliminary consideration of rheumatic fever in the doubtful case. Such diseases may be recognized by careful study of the clinical picture, by laboratory data, or, if necessary, by biopsy of material from muscle or skin lesions. Particularly confusing is the drug sensitivity with fever and polyarthritis which may occur after penicillin administration for a previous pharyngitis. The presence of cardiac abnormalities is indicative of rheumatic fever, while pruritic rash or urticaria tends to incriminate penicillin sensitivity. The subcutaneous nodule of rheumatic fever, although found in only 10% of cases, may be considered as a specific rheumatic lesion and should be looked for periodically in doubtful cases. The abdominal pain of patients with minimal articular symptoms may be difficult to differentiate from that of a surgical abdomen. Absence of muscular rigidity and localizing signs usually are sufficient to forestall operation until other evidences of rheumatic fever become manifest.

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In order to help clarify the diagnosis of rheumatic fever the American Heart Association has accepted and modified criteria usually referred to as "Jones criteria." These may be divided into "major," "minor," and "other manifestations." The finding of two major criteria or one major and two minor criteria indicates, as a rule, a high probability that rheumatic fever is present. The "other manifestations" may be used as supportive data. The criteria are not to be used as a substitute for good medical judgment but are recommended as a guide for careful study of questionable cases. The criteria are presented in table 3.

Treatment.—Treatment is directed chiefly to the prevention or suppression of carditis and its sequelae. Control of fever, cardiac pain, and polyarthritis are important not only for the comfort of the patient but also because their persistence indicates continuing activity which may heighten the possibility of cardiac damage. Joint involvement, however, does not lead to permanent arthritic damage. Bed rest is essential during the active phase, as is adequate nutrition.

A therapeutic course of penicillin should be promptly and routinely given in sufficient dosage to eliminate the possibility of any persistent hemolytic streptococcic infection. This should not be withheld even in a patient with negative throat cultures, as streptococci may be in inaccessible areas. Adequate blood levels of penicillin over a 10-day period are desirable. This may be achieved most readily by a single intramuscular injection of 1,200,000 units of benzathine penicillin. Other penicillin preparations may be used but they require multiple injections.

Both the adrenal glucocorticoids and the salicylates have potent antipyretic and anti-inflammatory action. Their relative merits and the value of either in preventing or minimizing permanent valvular scarring is still controversial, but there is evidence that both are valuable when given early and in adequate dosage. There is, however, usually no need to restrict therapy to a single agent and, when indicated by the presence of carditis, both corticoids and salicylates may be used to advantage. Either may produce undesirable collateral effects, but, as these are more frequent and potentially more serious with the adrenal steroids, their use makes closer observation of the patient necessary.

The risks of steroid therapy are discussed in more detail in the section on rheumatoid arthritis. Although the side-reactions outlined there may also be noted in patients with rheumatic fever, the relatively shorter period of administration makes their appearance less likely. A history of either peptic ulcer or psychotic tendencies weighs heavily against their use except as a lifesaving measure, but with these exceptions the drugs may be used if the usual precautions are observed.

It is, of course, impossible to specify exact dosage of medicaments in a disease as variable as rheumatic fever. However, the following general rules are useful: 1. The primary purpose of drug therapy is the prevention or minimizing of heart damage. 2. Combined salicylate and steroid therapy should be employed in the early stages, or later if there is evidence of acute cardiac involvement. 3. If the patient is seen more than two weeks after the onset of the disease, and neither pericarditis nor significant murmurs have developed, therapy with salicylates alone may be employed. However, since carditis may not be readily detectable in infants and young children, combined therapy is usually indicated.

Prednisone (or the equivalent of one of the other steroids having low sodium-retaining properties) dosage should approximate 10 to 15 mg. every six hours for two to three weeks, decreasing after that time as objective signs indicate subsidence of the inflammatory stage. The drug should not be decreased more rapidly than by 5 mg. every fourth to sixth day. The total period of steroid therapy will vary from 3 to 12 weeks, with a median of 6, depending on the severity of the presenting picture, the response to therapy, and the general reaction of the patient.

TABLE 3.—*"Jones" Criteria for Differential Diagnosis of Rheumatic Fever*

Major	Minor	Other Manifestations
Carditis	Fever	Weight loss
Polyarthritis	Arthralgia	Easy fatigability
Chorea	Prolonged P-R interval on electrocardiogram	Malaise
Subcutaneous nodules	Increased erythrocyte sedimentation, presence of C-reactive protein, or leukocytosis	Sweating
Erythema marginatum	Evidence of preceding beta hemolytic streptococcic infection	Pallor or anemia
	Previous history of rheumatic fever or presence of inactive rheumatic heart disease	Tachycardia when sleeping
		Erythema nodosum
		Precordial pain
		Abdominal pain
		Headache and vomiting

Salicylates are administered as acetylsalicylic acid or sodium salicylate (enteric-coated), 5 to 15 grains (0.3 to 1.0 Gm.) every four hours for a total daily dose approximating 2/3 grain per pound (40 mg. per 0.45 kg.) of body weight. Tinnitus may be unpleasant but is not considered dangerous; hyperventilation is an indication to decrease the dosage. The continuance of salicylate therapy for from one to four months after subsidence of clinical activity appears to decrease the possibility of "rebounds."

During the period of active disease bed rest is essential. Mobilization is begun cautiously when signs and symptoms of rheumatic activity have been absent for two to four weeks, and while salicylate medication is being continued. A return of rheumatic activity necessitates return to bedfast

status. Cardiac failure at any period is treated in the customary manner with rest, salt restriction, and administration of digitalis, diuretics, and oxygen.

The erythrocyte sedimentation rate appears to be the laboratory test of greatest value in determining rheumatic activity. Other tests for inflammation may in some instances be helpful but are rarely necessary. Serial electrocardiograms are necessary in following the cardiac status.

Prevention.—Perhaps the greatest contribution to the control of rheumatic fever has been the appreciation of the role of streptococcic infection as a causative agent of the disease. Recurrent attacks of rheumatic fever may be prevented by avoiding streptococcic infections, and this can be accomplished by giving 1,200,000 units of benzathine penicillin intramuscularly once each month. Prophylaxis can also be accomplished by giving 250,000 units of penicillin orally twice daily. The intramuscular injection is usually preferred, since it insures that the proper dose is administered. All patients under the age of 18 years should receive a continuous prophylactic regimen. In those over 18 years of age the program should be continued at least five years after each attack and longer if there is frequent exposure to children or other probable sources of streptococcic infection.

The early and adequate treatment of upper respiratory tract infection of streptococcic origin appears to eliminate the possibility of a rheumatic attack. A single injection of 1,200,000 units of benzathine penicillin intramuscularly would appear to be adequate in accomplishing this result. An alternate plan is the injection of 600,000 units of procaine penicillin in aluminum monostearate every third day for three doses. In children the latter dose may be reduced to 300,000 units.

Patients with rheumatic valvular disease contemplating dental extraction or surgical procedures should be given a prophylactic dose of 1,200,000 units of benzathine penicillin intramuscularly, even if they are on the prophylactic regimen previously outlined.

Prognosis.—The prognosis of rheumatic fever is extremely variable and depends primarily on the degree of cardiac embarrassment, which in turn is related to the number and severity of attacks. Unless accompanied by other signs of cardiac decompensation, the presence of a rheumatic heart murmur does not warrant severe restriction of physical activity, school work, or childbearing but is a sign for adequate supervision of such activities. In this regard the attitude of the patient is important, and psychological crippling due to the knowledge of the existence of heart murmurs must be avoided. Cardiac enlargement, congestive heart failure, or auricular fibrillation, on the other hand, carry a poor prognosis and are signals for definite restriction of activities. However, prophylaxis, early therapy of streptococcic infections, and adequate treatment of recurrent attacks may appreciably alter the outlook of the severely affected rheumatic patient. Cardiac surgery, while beyond the scope of this primer, may be the means of adding many years to the life of the patient with formerly hopeless rheumatic fever.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disease of connective tissue manifested by arthritic and consitutional symptoms of varying degree, not infrequently leading to permanent joint deformities and chronic invalidism. It is a universal disease, which, although most frequent in temperate climates, is found throughout the world. It may start at any age, from infancy to advanced years, but the age at onset will be between 25 and 50 years, in 80% of cases. Women are affected three times as frequently as men. Because of the common occurrence of the disease (2.7% of persons over 14 in a recent epidemiologic survey in Pittsburgh) the economic aspects are of extreme importance. Affecting, as it is prone to do, young adults, it may seriously impair the earning power of the household provider, or so radically interfere with the activities of a young mother as to make childbearing and child-rearing a grave problem. As older persons become invalided from the disease their physical and financial care may wreak great hardships on other members of the family, as well as presenting psychological problems of major importance.

Etiology.—Rheumatoid arthritis is a disease of unknown cause. Many hypotheses of its nature have been entertained—infection, endocrine imbalance, hypersensitivity, and faulty adaptation to either physical or psychic stress, among others—but proof for any one of these is lacking at the present time. It has a slight tendency to be familial. Clinical and pathological changes, comparable to those of rheumatoid arthritis, occur in appreciable numbers of patients with other so-called collagen diseases, particularly systemic lupus erythematosus and polyarteritis nodosa. Whether these disorders are fundamentally related to each other or are coexisting separate entities has not been established.

Pathology.—Rheumatoid arthritis is invariably described as a systemic disorder. Constitutional manifestations of fever and asthenia, with laboratory evidences of inflammation, are usually present during acute stages of the diseases. Nevertheless it is the joint changes which characterize the disease, and extra-articular lesions cannot be demonstrated consistently. When present, the individual changes are for the most part lacking in diagnostic specificity.

Articular Lesions: The articular lesions vary greatly with the stage and severity of the disease. The earliest changes are recognized in the synovial tissue lining the articular cavities. They are of a nonspecific inflammatory type, including congestion, edema, exudation of fibrin and leukocytes,

formation of granulation tissue, and infiltration with chronic inflammatory cells. As a result, the synovial tissue may become greatly thickened with villous hypertrophy. As the disease progresses, the peripheral portions of the articular cartilage are involved in the inflammatory reaction and undergo lysis, with replacement by granulation tissue. Comparable inflammatory changes frequently are present in the subchondral marrow spaces. The adhesive granulation tissue extending from the synovial lining across the cartilage is referred to as a pannus. As it progresses, the articular surface of the bone may be destroyed and rarefaction of the juxtaarticular bone may develop. The majority of the infiltrating inflammatory cells are lymphocytes and plasma cells. They are distributed both diffusely and in focal nodular aggregates. Although these synovial changes are characteristic of rheumatoid arthritis, they may be seen in other chronic joint diseases. In addition to these nonspecific changes, focal lesions that resemble the more specific granuloma-like nodules present in the subcutaneous tissue and elsewhere may at times be found.

As the disease progresses adhesions may form between the apposing surfaces of granulation tissue. Cicatrization and metaplasia of the granulation tissue may result variously in fibrous, cartilaginous, and bony ankylosis. Severe deformity of the joints may arise both from inflammatory destruction of the joint surface and from involvement of the adjacent tendons.

Subcutaneous Nodules: Although seen in only 15 to 20% of cases, the subcutaneous nodules of rheumatoid arthritis demonstrate the most characteristic histological lesion of the disease. The nodules have granuloma-like features. Within the nodules three elements are recognized: a central zone of "fibrinoid" necrosis of collagenous tissue; a surrounding palisade of radially arranged, elongated connective tissue cells; and a periphery of chronically inflamed granulation and fibrous tissue. There is some evidence that inflammation of blood vessels plays a primary role in the development of these nodules. In general, they are similar to the subcutaneous nodules of rheumatic fever but show more necrosis and fibrosis. The differences have been explained on the basis of the greater duration and size of the rheumatoid lesion. On rare occasions, nodules are seen in persons not known to have rheumatoid arthritis.

Heart: Although not often apparent clinically, evidences of heart disease have been found with some frequency at autopsy in patients with rheumatoid arthritis. Pericarditis has been seen in 25 to 40% of cases. There are conflicting reports of the occurrence of valvular lesions resembling those of rheumatic fever, the figures varying from 12 to 65% of patients with rheumatoid arthritis coming to autopsy. Within recent years there has emerged a concept of specific rheumatoid heart disease characterized not only by pericarditis, myocarditis, and coronary arteritis but also by granulomatous inflammation of the heart valves, comparable to that of the subcutaneous nodules. These lesions are only infrequently of sufficient magnitude to be apparent clinically.

Arteries: Inflammation of isolated small arteries has been demonstrated in appreciable numbers of patients with peripheral rheumatoid arthritis. The arteritis has a variable character, often being mild and of limited extent. At times, however, the lesions may be associated with peripheral neuropathy or systemic polyarteritis nodosa. It has been suggested that severe vascular changes are more frequent in patients treated with large doses of steroid compounds than in untreated patients.

Miscellaneous Lesions: Focal infiltrations of lymphocytes occur in the skeletal muscles in the majority of patients with rheumatoid arthritis but cannot be regarded as pathologically specific. Atrophy of muscle fibers is common but degeneration is infrequent. Hyperplasia of lymph nodes may occur in the regions of affected joints but is occasionally generalized. The changes are nonspecific and are not to be confused with giant follicular lymphadenopathy. Chronic scleritis, at times with uveal herniation (scleromalacia perforans), is an infrequent lesion and resembles the subcutaneous granuloma. Nonspecific iridocyclitis occurs commonly in juvenile rheumatoid arthritis and ankylosing spondylitis and less frequently in peripheral rheumatoid arthritis. Granulomatous nodules are found infrequently in the lungs and pleura, as in other viscera. Secondary amyloidosis has been reported in approximately 20% of autopsies on patients hospitalized for rheumatoid arthritis.

Clinical Features.—Although the crippled patient with far-advanced rheumatoid arthritis presents a characteristic picture, the onset and course of the disease are subject to wide variations. Constitutional symptoms of generalized weakness, fatigue, and morning stiffness may precede the articular manifestations but are usually mentioned by the patient only in retrospect. With few exceptions, the joint symptoms form the initial complaint.

In 75 to 80% of the cases the onset is insidious. The patient may awaken one morning with one or more joints sore and stiff. As the day progresses these become moderately inflamed, with modest swelling, redness, and soreness. These symptoms may persist for several days or even several weeks. Indeed, stiffness and pain may be present before demonstrable swelling is noted, and, although swelling appears, other signs of inflammatory reaction such as redness and warmth may be lacking. Within a period varying from several days to several months other joints may become similarly involved. In the majority of cases, rheumatoid arthritis is a progressive disease and once begun

does not entirely subside. Symptoms and signs in articulations involved may resolve completely, subside partially, remain undiminished, or develop acute (and often severe) exacerbations. Despite this tendency to chronicity, periods of spontaneous remission may occur during which the patient is relatively asymptomatic. Usually, however, these remissions are not complete. Further exacerbations occur and, as time progresses, various deformities may ensue.

In contrast to this mode of onset, approximately 20 to 25% of the cases are ushered in by a fulminating phase in which one or more joints abruptly become markedly swollen, painful, and tender with localized heat and inflammation. A migratory type of polyarthritis simulating rheumatic fever may then persist for several days or weeks. Some of these fulminant cases progress to severe deformities within a matter of weeks, often in spite of active therapy. Usually, however, this phase will subside after several weeks, the case then progressing to the more usual chronic course of exacerbations and remissions.

Any diarthrodial joint in the body, including the temporomandibular and sternoclavicular, may be involved. In the hands the proximal interphalangeal joints are particularly prone to be affected, and, as they enlarge, the fingers develop a characteristic fusiform appearance. The metacarpophalangeal articulations of the index and middle fingers are also peculiarly susceptible. In Army hospitals a high percentage of cases are found to start in the feet. As the disease progresses, deformities of varying degree may be encountered. Probably the most frequent are those of the hand, involvement at the metacarpophalangeal level resulting in flexion and ulnar deviation of the fingers. Volar subluxation of the carpus, imperfect extension of the elbows, and partially flexed knees are further examples of this situation. In cases of advanced disease contractures, bony ankyloses, subluxations, or dislocations of joints may occur. Muscular weakness and atrophy may be prominent.

The skin of the extremities may become smooth, glossy, and atrophic (sclerodactylia). There may be redness of the thenar and hypothenar eminences, while the hands are often cold and clammy.

When present, subcutaneous nodules are found most frequently over the extensor surface of the proximal third of the ulna, distal to the olecranon process, but they may be widespread in the region of bony prominences and in superficial tendons. They vary from scarcely palpable seed-like particles to lesions 3 to 5 cm. in diameter. Usually not painful, they may occasionally ulcerate and become secondarily infected if subjected to undue pressure. Having once appeared, they usually persist throughout the disease, although they may decrease in size and some even disappear during a lengthy remission.

Constitutional symptoms of weakness and fatigue in varying degrees are common throughout the course of the disease. In addition, during periods of acute fulminating joint involvement there is likely to be malaise, fever, and anorexia. It is, however, a matter of interest that profound joint changes may occur in healthy, robust persons.

Splenic enlargement occurs in approximately 5 to 10% of patients and may be associated with leukopenia (sometimes called Felty's syndrome). Generalized lymphadenopathy of moderate degree is commonly observed. Joint changes resembling rheumatoid arthritis occur in 4 to 5% of patients with ulcerative colitis.

One of the still unresolved riddles in this complex condition pertains to the exact delineation of the role played by emotional and psychological reactions in the etiology and course of the disease. A high percentage of patients will exhibit a passive, dependent personality, with frequent periods of hostile aggression toward family, physician, and associates. Yet this is by no means universal, and rheumatoid arthritis will be found in patients with all personality patterns. Still, the frequency with which exacerbations of the disease are related to periods of major emotional stress cannot be ignored. Further contributing to this problem is the fear reaction engendered by the victim's realization of the consequences of a chronic, potentially incapacitating disease. Thus, whether they be cause or effect or a combination of both, psychological reactions early assume a place of importance in the disease state.

Diagnosis.—Although far-advanced cases of rheumatoid arthritis are easily recognized, the protean nature of the early disease may make definite diagnosis difficult. Rheumatic fever, gout, disseminated lupus erythematosus, and osteoarthritis will cause the greatest confusion.

Rheumatic fever may simulate rheumatoid arthritis during the early acute inflammatory stages when both may present a migratory polyarthritis. The differential diagnosis is discussed above.

Although gout may cause some confusion, the acute severe monarticular self-limiting episodes usually distinguish it from the less acute polyarticular involvement of rheumatoid arthritis. The favorable therapeutic response to colchicine, so characteristic of early acute gout, does not occur in rheumatoid arthritis. Hyperuricemia aids in confirmation of the diagnosis of gout. Biopsy of synovial tissues or suspected tophi may at times be of assistance.

Systemic lupus erythematosus may be indistinguishable from rheumatoid arthritis and, indeed, it is still uncertain whether the two at times coexist or are part of the same general disease process. However, patients with lupus erythematosus usually show only minimal articular symptoms but severe

constitutional manifestations with visceral involvement and the characteristic L. E. cell phenomenon.

Joint symptoms occurring in middle-aged patients may cause some difficulty in differentiation between rheumatoid arthritis and osteoarthritis. The presence of inflammatory signs usually indicates rheumatoid arthritis, although this is not always the case. Osteoarthritis is more prone to be localized to one or two joints, whereas rheumatoid arthritis involves multiple joints. In the hands, involvement of the proximal interphalangeal joints suggests rheumatoid arthritis and that of the distal interphalangeal joints, osteoarthritis. An accelerated erythrocyte sedimentation rate and serologic reactions may be of aid in diagnosis. In order to assist in the differential diagnosis, the American Rheumatism Association has adopted the following criteria for diagnosis of this disease.

Classic Rheumatoid Arthritis

The diagnosis of classic rheumatoid arthritis requires the satisfaction of seven of the following criteria. In criteria 1 through 5 the joint signs or symptoms must be continuous for at least six weeks (any one of the features listed under "Exclusions" will exclude the patient from this category).

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid, not bony overgrowth alone) in at least one joint (observed by a physician).
4. Swelling (observed by physician) of at least one other joint (intervals free of joint symptoms between the two joint involvements of not more than three months).
5. Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of the midphalangeal, matacarpophalangeal, or metatarsophalangeal joints is acceptable, without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces, or in juxta-articular regions.
7. Roentgenographically visible changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes). Degenerative changes do not exclude the diagnosis of rheumatoid arthritis.
8. Positive result of agglutination test—demonstration of the "rheumatoid factor" by any method which, in two laboratories, has been positive in not over 5% of normal controls—or positive result of streptococcic agglutination test.
9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
10. Characteristic histological changes in synovial membrane, with three or more of the following findings: marked villous hypertrophy; proliferation of superficial synovial cells, often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating), with tendency to form "lymphoid nodules"; deposition of compact fibrin, either on surface or interstitially; or foci of cell necrosis.
11. Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Definite Rheumatoid Arthritis

The diagnosis of definite rheumatoid arthritis requires the satisfaction of five of the above criteria. In criteria 1 through 5 the joint signs or symptoms must be continuous for at least six weeks (any one of the features listed under "Exclusions" will exclude a patient from this category).

Probable Rheumatoid Arthritis

The diagnosis of probable rheumatoid arthritis requires the satisfaction of three of the above criteria. In at least one of criteria 1 through 5 the joint signs or symptoms must be continuous for at least six weeks (any one of the features listed under "Exclusions" will exclude a patient from this category).

Possible Rheumatoid Arthritis

The diagnosis of possible rheumatoid arthritis requires the satisfaction of two of the following criteria and total duration of joint symptoms must be at least three weeks (any one of the features listed under "Exclusions" will exclude a patient from this category).

1. Morning stiffness.
2. Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for three weeks.
3. History or observation of joint swelling.
4. Subcutaneous nodules (observed by a physician).
5. Elevated sedimentation rate or C-reactive protein level.
6. Iritis.

Exclusions

Any one of the following clinical features constitutes an exclusion from each of the diagnoses listed above.

1. The typical rash of disseminated lupus erythematosus (with butterfly distribution, follicle plugging, and areas of atrophy).
2. A high concentration of lupus erythematosus cells (four or more in two smears prepared from heparinized blood incubated not over two hours).

3. Histological evidence of polyarteritis nodosa, with segmental necrosis of arteries, associated with nodular leukocytic infiltration extending perivascularly and tending to include many eosinophils.

4. Weakness of neck, trunk, and pharyngeal muscles or persistent muscle swelling or dermatomyositis.

5. Definite scleroderma (not limited to the fingers).

6. A clinical picture characteristic of rheumatic fever with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules, erythema marginatum, or chorea (an elevated antistreptolysin titer will not rule out the diagnosis of rheumatoid arthritis).

7. A clinical picture characteristic of gouty arthritis, with acute attacks of swelling, redness, and pain in one or more joints, especially if relieved by colchicine.

8. Tophi.

9. A clinical picture characteristic of acute infectious arthritis of bacterial or viral origin, with an acute focus of infection or in close association with a disease of known infectious origin; chills; fever; or an acute joint involvement, usually migratory (especially if there are organisms in the joint fluid or the patient responds to antibiotic therapy).

10. Tubercle bacilli in the joints or histological evidence of joint tuberculosis.

11. A clinical picture characteristic of Reiter's syndrome, with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.

12. A clinical picture characteristic of the shoulder-hand syndrome, with unilateral involvement of shoulder and hand and diffuse swelling of the hand followed by atrophy and contractures.

13. A clinical picture characteristic of hypertrophic pulmonary osteoarthropathy, with clubbing of fingers or hypertrophic periostitis along the shafts of long bones, or both, especially if an intrapulmonary lesion is present.

14. A clinical picture characteristic of neuroarthropathy, with condensation and destruction of bones of involved joints and associated neurological findings.

15. Homogentisic acid in the urine detectable grossly with alkalinization.

16. Histological evidence of sarcoid or a positive result of the Nickerson-Kveim test.

17. Multiple myeloma as evidenced by marked increase in plasma cells in the marrow or Bence Jones protein in the urine.

18. The characteristic skin lesions of erythema nodosum.

19. Leukemia or lymphoma, with characteristic cells in peripheral blood, marrow, or tissues.

20. Agammaglobulinemia.

Laboratory Findings.—During active stages of the disease results of the several nonspecific tests for inflammation are usually positive: elevated erythrocyte sedimentation rate, C-reactive protein, and, occasionally, mild leukocytosis. The serum in most cases of peripheral rheumatoid arthritis has the ability to agglutinate or flocculate a variety of suspended particles, hemolytic streptococci, sheep red blood cells sensitized with amboceptor (anti-sheep erythrocyte rabbit serum), and latex and bentonite suspensions, among others. These phenomena apparently depend on the presence of abnormal macroglobulins in the serum. Several serologic tests based on this reaction have a high degree of diagnostic specificity (approximately 85%). They usually give negative results in patients with ankylosing spondylitis, juvenile rheumatoid arthritis, and psoriatic arthropathy. Generally accepted positive titers are sheep cell agglutination, 1:32; bentonite flocculation, 1:32; and latex particle fixation, 1:20. These agglutination reactions may not be positive, however, during the first several weeks or months of the disease, when the differential diagnosis is most difficult.

The serum globulin concentration is elevated, at least relative to the value of serum albumin. Normocytic, hypochromic anemia, refractory to iron, is commonly present during the active phases of rheumatoid arthritis. The serum uric acid concentration is usually within normal limits, as is the antistreptolysin-O titer. The synovial fluid tends to be turbid and may clot spontaneously in vitro. Its viscosity is reduced. The fluid contains an excess of leukocytes, their number varying in proportion to the severity and acuteness of the process. During acute episodes polymorphonuclear leukocytes predominate; during more quiescent periods lymphocytes are more numerous. When acetic acid is added to the synovial fluid the normal ropy mucin clot fails to appear.

Prognosis.—Because of the dramatic appearance of the severely crippled patient with rheumatoid arthritis the gravity of the prognosis in rheumatoid arthritis is commonly exaggerated. Actually, patients with mild cases may recover spontaneously and lengthy remissions in which the disease is apparently arrested may occur even in those of many years' duration. Furthermore, with proper therapy, the more severe consequences of the disease may be lightened or entirely prevented in the majority of cases.

Treatment.—Despite the lack of specific therapeutic agents, it is usually possible to control the disease or ameliorate its manifestations. However, the natural history of the disease, with spontaneous remissions and exacerbations, and the prominent psychological factors notable throughout the disease, make evaluation of individual therapeutic modalities difficult.

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It would seem most convenient to classify the various treatment methods in six general categories: (1) general measures, (2) drug therapy, (3) physical therapy, (4) steroid therapy, (5) orthopedic measures, and (6) psychotherapy.

General Measures: Since arthritis is a systemic disease for which no specific cure has been found, it follows that all those general measures which will improve the patient's health, so that his natural protective resources may function optimally, must be employed to their utmost. The first of these is rest, systemic and local. Because the disease affects the muscles the patient will fatigue easily and will therefore need more general rest than the unaffected person. During acute fulminating periods complete bed rest may be indicated. Local rest, particularly in severe exacerbations, may be accomplished by splinting. During such periods at rest precautions must be taken to prevent further muscle wasting and ankylosis of joints. Toward this end active physical therapeutic measures are indicated, as will be noted below. The occasional use of sedatives at night is justified. Closely allied with rest is the matter of exercise. Patients should be taught the value of simple setting-up exercises and deep breathing exercises to help strengthen the general muscular tone, as well as specific exercises for involved limbs.

A well-balanced diet is indicated, no individual food or vitamin having been found beneficial or detrimental. Patients should be cautioned to wear warm clothing and to protect their joints, especially in cold or rainy seasons, and to avoid undue chilling and drafts. Temporary improvement in symptoms during spa therapy would appear to be related to favorable changes in environment, coupled with judicious administration of physical therapy. Foci of infection should be removed if they impair general health.

Drug Therapy: Salicylates remain the most useful drugs in the treatment of rheumatoid arthritis. All are approximately therapeutically equal, usually cheap, readily available, and well tolerated. Aspirin —plain, coated, or buffered—is the preferred drug. One to three 5-grain (325-mg.) tablets or their equivalent may be administered two to six times per day, depending on the severity of the condition. Maximum doses to the point of mild salicylism may be required for the relief of pain. Some physicians prefer to govern the dose by estimations of the serum level of salicylate, 25 mg.% being the level usually desired.

Recently developed non-narcotic analgesics have also proved helpful as pain-relieving adjuncts to therapy. Barbiturates and other sedatives may be prescribed as indicated. Treatment with codeine and other narcotics should be assiduously avoided.

Phenylbutazone has proved to be of limited benefit as an antirheumatic agent in rheumatoid arthritis. It is administered orally, 200 to 600 mg. per day. Potentially toxic properties include depression of marrow, with resultant decrease in formed blood elements; gastrointestinal irritation, with peptic ulcer and gastrointestinal bleeding; and allergic skin reactions. Although comparatively rare, when compared to the total number of cases treated thereby, nevertheless these serious side-reactions from phenylbutazone must be borne in mind. Blood counts and urinalyses should be done after the first week of therapy and then at four-week intervals. A patient who has not shown a prompt response (within 10 to 14 days) to an adequate dose of the drug will not respond to prolonged administration, and the medicament should then be discontinued.

Antimalarial compounds, such as chloroquine phosphate and hydroxychloroquine sulfate appear to suppress rheumatic activity in some patients with rheumatoid arthritis; the former in doses of 250 to 500 mg. per day and the latter in doses of 200 to 400 mg. The beneficial effects of these drugs are slow to develop, usually being noted only after three to six weeks of therapy. However, once improvement develops it is usually sustained. Toxic reactions, such as blurring of vision, nausea, anorexia, leukopenia, or dermatitis, develop in some patients, occasionally necessitating discontinuance of the drug.

Soluble gold compounds have been found useful in the treatment of many patients with rheumatoid arthritis. Their beneficial effect appears to be attendant on suppression and even arrest of the active rheumatoid process, whereby lengthy remissions may be induced. There is, however, no reversal of established deformities. Therefore, gold compounds are most effective in the early and active stages of the disease, but remissions have been induced even in long-standing cases. The palindromic variant of rheumatoid arthritis appears particularly susceptible to the beneficial effect of chrysotherapy.

The preparations of gold which have been found most dependable are gold sodium thiosulfate, gold sodium thiomalate, and gold thioglucose. All are given by intramuscular injection, usually at weekly intervals, in doses of 25 to 50 mg. The first injection is usually of 10 mg., as a test for toxicity. Subsequent doses are increased to the maintenance level. This is then continued until one of three responses is noted: (1) toxic reactions which may require discontinuance or interruption of the drug; (2) therapeutic nonreactivity, which is felt to occur if the patient notes no improvement after approximately 10 to 12 injections; or (3) adequate therapeutic response. This will usually occur between the 8th and 15th injection, at which time the inflammatory manifestations have decreased and the sedimentation rate has shown a significant drop. The injection of gold is then given every second

week, and, as improvement continues, every third and finally every fourth week. It is continued at this interval until maximum remission, with normal sedimentation rate, has been noted for at least four months. To maintain such remissions monthly or bimonthly injections may be continued indefinitely, for as long as three to five years. During this period, if there is an exacerbation of symptoms, weekly injections are reinstituted according to the former program. The drug therapy is discontinued when the joints have been asymptomatic and the sedimentation rate normal for six months.

Unfortunately, serious reactions to gold may occur at any time during its administration; the appearance of these is a signal to limit or discontinue the treatment. These include dermatitis (the most common), blood dyscrasias, stomatitis, hepatitis, colitis, and hematuria. Prior to the institution of therapy each patient should be cautioned that such reactions may occur and should be told to advise the physician of the appearance of any skin rash. A small percentage of patients will note a flare-up of the arthritic process 24 to 48 hours after the administration of gold. This may usually be overcome by decreasing the size of the dose and concurrently administering antihistaminic drugs. Weekly estimations of the hemoglobin or hematocrit level, a white blood cell count, and a check of the urine for albumin should be done during the early stages of gold administration and at least once a month as it is continued. The appearance of any rash or significant blood or urine alteration during the administration is a signal to lower the dose or discontinue therapy. British anti-lewisite (BAL) has been helpful in instances of severe reaction, but undesirable effects may accompany the use of this compound, too. Corticosteroids or corticotropin are reliable and effective in controlling many of the undesirable reactions.

The acute inflammatory phase of rheumatoid arthritis may at times be controlled by the intravenous administration of either nitrogen mustard or typhoid vaccine. Remissions induced thereby are temporary, necessitating additional "follow-up" therapy with use of other modalities.

Physical Therapy: Physical therapy is of value in all stages of rheumatoid arthritis. During acute episodes local applications of warm moist compresses will assist in relieving inflammation and alleviating pain. These are also useful preceding periods of passive exercise.

In treating patients with more chronic cases a comprehensive program should be outlined by the physician (preferably a physiatrist). This may frequently be carried on by the patient at his home, with progress noted at specified intervals in the physician's office. The program will include one or two daily periods of active exercise, usually preceded by applications of heat in the form of infrared radiation. Exercises prescribed should include general ones designed to maintain proper posture and weight-bearing alignment as well as local ones to strengthen muscles and prevent or correct deformities. It is usually advisable from time to time to supplement this home program with professional physical therapy. On these occasions more active measures such as muscle massage, resistive exercises, and gentle muscle stretching may be indicated. Care must be observed to avoid forcing joints beyond their limit and thereby reactivating a latent process.

Steroid Therapy: Although corticosteroids do not basically alter the fundamental pathological process in rheumatoid arthritis, their judicious therapeutic use may be of material assistance in the management of patients resistant to other modes of therapy. The administration of adequate amounts of these hormones to patients with active rheumatoid arthritis results in dramatic alleviation of symptoms and signs, with prompt relief of pain and stiffness, reduction of fever, and reversal of certain abnormal laboratory findings (lowering of erythrocyte sedimentation rate, increase in serum albumin and decrease in serum globulin levels, improvement in anemia, and correction of synovial fluid abnormalities). The remarkable psychological improvement which many patients experience when first receiving these agents is noteworthy. This is often of considerable importance in easing the problem of nursing care and assisting in more effective acceptance of physical therapy and other general measures in management. Since the action of these drugs is one of suppression of inflammatory reactions rather than eradication of the basic causative mechanism, these benefits persist only as long as an adequate dose of the hormone is maintained and there is no increased tendency to natural remission of the disease process itself. It is therefore apparent that, if these are used in treatment of rheumatoid arthritis, administration over protracted periods of time will be necessary.

The chief difficulty attendant on the continued use of high doses of steroids pertains to those metabolic activities which eventually lead to a series of untoward side-effects resembling adrenocortical hyperfunction (Cushing's syndrome). These vary from the minor annoyances of moonface, acne, hirsutism, euphoria, fat deposition, weight gain, dyspepsia, and sleeplessness to the major complications of peptic ulcer, osteoporosis and pathological fractures, edema due to sodium and water retention, frank psychosis, hypopotassemia and muscle weakness, hypertension, glycosuria and hyperglycemia, ecchymosis, and the reactivation of such latent infections as tuberculosis. Although these are apparently rare, the use of steroid therapy in patients with rheumatoid arthritis may be associated with an increased incidence of necrotizing angiitis and peripheral neuropathy. Furthermore, continued use of steroids leads to temporary

atrophy of the patient's own adrenal cortex, and apparently to certain portions of the pituitary gland also. It is therefore imperative to increase the steroid dosage when the patient is subjected to additional stress, as when undergoing surgery. Since 10 to 12 months may be required for complete restoration of adrenal function after the cessation of steroid therapy, such administration of supplemental hormones during episodes of stress may be required in this period.

In action and side-effects all the synthetic hormones are remarkably similar to their natural precursors, but when used in comparable therapeutic doses they have less tendency to promote retention of sodium and water. Accordingly their use is less frequently marred by the development of peripheral edema and hypertension. However, abdominal bloating, peptic ulcer, and increased capillary fragility, with ecchymotic areas of the extremities, are more common with these than with cortisone. All the adverse reactions noted are related to the size of the dose administered and the length of time it is continued. There is, however, a marked variation from patient to patient, and many can tolerate considerably higher doses over longer periods of time than their less fortunate co-sufferers. Much attention continues to be given to further modification of chemical structure, in an attempt to produce an "ideal steroid," and it seems reasonable to assume that one may be developed which will have antiphlogistic powers, without other metabolic effects.

Steroid therapy should therefore be reserved for those patients in whom the rheumatoid process is showing continuing activity despite an adequate trial on the simpler programs of management previously outlined in this primer. The coexistence of certain other conditions, such as active tuberculosis or other systemic infections, severe diabetes mellitus, peptic ulcer, and advanced hypertensive vascular disease, must serve as relative contraindications to their use, although in some instances appropriate therapy for these complications will permit steroid therapy to proceed without untoward incident.

The formidable risk of adverse reactions has served to limit attempts to achieve a complete suppressive effect through the administration of large doses; rather, it seems wise to regulate the daily dose to that level which will permit the patient some relief of pain and a corresponding increase in physical activities and to maintain this level over as long a period of time as possible. This can usually be obtained by the administration of approximately 37.5 to 50 mg. of cortisone per day or its equivalent in one of the synthetic hormones (10 to 12 mg. of prednisone or prednisolone, 6 to 10 mg. of triamcinolone or methylprednisolone, or 0.75 to 1.5 mg of dexamethasone). Alterations in the daily dose are accomplished extremely slowly (an increase or decrease of 2.5 to 5 mg. of cortisone or its equivalent every third to fifth day), because more rapid withdrawals may precipitate severe exacerbations of the disease. The concurrent administration of adequate doses of salicylates will usually assist in maintaining clinical control.

The local (intra-articular) injection of hydrocortisone or other steroids continues to prove useful in those patients with rheumatoid arthritis in whom active disease is confined to one or two joints or in whom involvement of a single joint is so disproportionately severe as to limit the effectiveness of the entire treatment program. Virtually any of the peripheral articulations may be injected, provided the physician is properly acquainted with the anatomic landmarks involved. Injections may be given two or three times a week during severe inflammatory periods and decreased as joint improvement occurs. With repeated injections the risk of joint infection is increased.

Orthopedic Measures: Application of splints and surgical procedures are of value in managing specific aspects of this disease. The immobilization provided by a light splint will aid in relieving the severe pain of an acutely inflamed joint as well as promote subsidence of the inflammatory reaction. However, to avoid the formation of adhesions within the joint, the splint should be removed daily, with the joint then passively carried through range-of-motion exercises. Splints are also useful for the prevention and correction of joint deformities. Those made of light aluminum are especially valuable for the hands, but for other joints deep "gutter" splints of plaster are preferable. These are generally worn all night but during only part of each day, in order to prevent the complications of disuse. When flexion contractures have occurred, plaster casts made in increasing extension combined with physical therapy may help to correct the contracture. Although the above measures will usually maintain joint function, if they fail and ankylosis appears inevitable the affected joint should be maintained in a position for optimal use. The knee should be kept extended to 180 degrees; the hip in slightly flexed position; the wrist in middorsal flexion, halfway between pronation and supination; and the elbow flexed at 90 degrees. Although prevention of deformities through the above measures is of the utmost importance, when deformities due to ankylosis or contractures have occurred selected patients may benefit from surgical correction of the deformity after the activity of the disease has subsided.

Psychotherapy: In view of the psychological factors previously mentioned it is apparent that a successful program of therapy must include consideration of the patient's personality pattern. This can usually be accomplished through sympathetic but firm management on the part of the attending physician; only rarely will formal psychiatric

assistance be indicated. Even then it may not be possible, for the patient may reject the suggestion of a psychic component in his illness, laying the blame for obvious emotional outbursts on the disease rather than on his own inadequacies.

The physician must therefore impart to the patient a sense of ultimate security, acting as the crutch to be leaned on in time of need or the alter ego to be railed at in times of despair. Sympathetic attention to the patient's complaints during the initial and subsequent interviews may not only uncover underlying hostilities amenable to correction but may foster a feeling of confidence in the physician's interest as well as his abilities. The need for, and rationale of, prescribed modalities must be carefully outlined so as to insure continuity of the program. Eventually, the patient's appreciation of his own part in the entire regimen may become the greatest single factor in his improvement.

Summary of Therapy.—Because of the marked variability of the disease pattern and the lack of specific therapeutic agents, a dogmatic attitude cannot be assumed toward therapy. However, the gratifying results to be achieved by a comprehensive regimen justify an optimistic approach to the care of the patient with rheumatoid arthritis.

A conservative regimen, including adequate doses of salicylates, physical therapy, and the "general measures" previously outlined, will be sufficient to control cases of mild and moderate severity.

Continuing rheumatic activity in spite of such a program is an indication for additional measures. If this activity is not great, treatment with phenylbutazone or chloroquine may bring about control. Patients with more severe cases will probably require treatment with gold. During periods of acute fulminating activity intravenous administration of typhoid vaccine or nitrogen mustard may be helpful. Patients whose conditions show progressive deterioration in spite of these measures should be judiciously treated with steroids.

It is thus evident that the therapeutic regimen may be altered as the disease state changes. It seems wise to acquaint the patient with this eventuality during early interviews so as to forestall later doubts about the adequacy of the program. Regardless of the apparent status of the condition at any particular time, regular examinations are indicated, with frequent counseling.

The concept of rehabilitation in rheumatoid arthritis must embrace all phases of the patient's therapeutic program, including discussion with the family of adjustment of the daily work load. In mild cases this may mean only the giving up of certain minor activities so as to find time for the rest and exercise period. In others, it may mean locating work for a previously inactive patient so as to impart new interest and sense of worth. In still others, it may mean installation in home or office of devices to assist the arthritic cripple in caring for himself as much as possible. Constantly to be borne in mind is the fact that the ultimate objective of therapy is not only to control the disease process but also to make the sufferer a self-respecting and useful member of society.

Rheumatoid Arthritis of the Spine

Synonyms for rheumatoid arthritis of the spine include ankylosing spondylitis, rheumatoid spondylitis, Marie-Strümpell disease, pelvospondylitis ossificans, spondylitis ankylopoietica, and spondylitis rhizomelique. Ankylosing spondylitis is a chronic inflammatory disease of the joints of the axial skeleton, manifested clinically by progressive stiffening of the spine and pain of varying degree. Because the earliest pathological change is synovitis of the axial diarthroses, comparable to that seen in the appendicular joints in rheumatoid arthritis, the American Rheumatism Association has classified this condition as rheumatoid arthritis of the spine. There are, however, significant differences from peripheral rheumatoid arthritis and because of these many rheumatologists regard it as a separate entity. This accounts for the many names by which the disease has been known.

Etiology.—The cause of the disease is unknown. Although it is frequently suspected, infection has not been proved. It is influenced by age and sex factors, occurring 10 times as commonly in men as in women and having its onset almost invariably before the age of 50 years.

Pathology.—Two apparently separate pathological processes distinguish this form of arthritis. The first of these is a synovitis of the spinal diarthroses similar to that described in the section on peripheral rheumatoid arthritis. In the majority of cases this occurs first in the sacroiliac joints and progresses to the apophysial joints (articulating facets) of the lumbar spine and thence to the thoracic and finally to the cervical spine. As the thoracic spine is attacked the costovertebral and costotransverse articulations are also affected. The degree of involvement of the various joints shows a wide range of variations; in the sacroiliac joints complete obliteration is common, and some apophysial joints may be spared entirely.

The second pathological change involves the intervertebral fibrocartilages, in which the annulus fibrosis becomes gradually ossified, fusing the vertebral bodies into a rigid unit. The subcutaneous nodules of rheumatoid arthritis are not seen in ankylosing spondylitis unless peripheral rheumatoid arthritis is also present. Insufficiency of the aortic valve has recently been recognized as an infrequent but specific lesion of ankylosing spondylitis. It is characterized by destruction of the media of the root of the aorta and consequent separation of the commissures of the valve.

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Clinical Course.—At least three-fourths of the cases start in the sacroiliac joints, with pain first identified in the lower part of the spine. As the disease progresses cephalad, the discomfort is noted at increasingly higher levels. Approximately 75% of the cases start gradually, with pain and stiffness coming on so insidiously that the patient may have difficulty later recounting the exact time of onset. Recurring sciatica is the initial complaint in approximately 10%, while the remaining 15% appear as an acute disease with an abrupt onset. This is characterized by generalized symptoms of weakness, fever, malaise, and weight loss and local symptoms of severe pain, tenderness, and stiffness usually involving the entire thoracic and lumbar spine. Such cases may pursue a rather rapid downhill course, with increasing general incapacity. In others the acute exacerbation may be aborted, and the case may then progress to a chronic course similar to those of insidious onset. Remissions and exacerbations are common. Arrest of the disease, either spontaneously or coincidentally with therapy, may occur at any time, or the disease may progress until it has involved the entire spine with ankylosis and deformity. Radicular symptoms may occur. When the disease affects the lower part of the spine, sciatica may be a manifestation of such a condition, whereas involvement of the spine at higher levels may give rise to symptoms simulating involvement of abdominal and thoracic viscera.

The most common physical finding in rheumatoid spondylitis is the rigidity of the spine. In the early cases this is noted only in the lumbar region; as the disease progresses it may involve the entire spine. Limitation of chest expansion, due to involvement of the costotransverse and costovertebral articulations, may occur early in the disease. In the lumbar spine the loss of the normal lumbar curve is frequently noted, while in the thoracic spine increase in upper thoracic kyphosis is common. When the cervical spine is involved the normal head motions are limited and the patient finds it necessary to rotate his entire body from the hips and to look out of the corner of his eyes in order to see from side to side. In the acute stages there is pain on pressure over the affected areas and muscle spasm on standing. Despite marked involvement of the spine, however, many patients retain general robust health. In others, usually those who have suffered frequent acute exacerbations, there is generalized weight loss and muscular wasting. Acute inflammatory reaction in the peripheral joints occurs in 50 to 60% of cases of rheumatoid spondylitis at some time during the disease. In at least one-half of these the peripheral symptoms are transitory and self-limiting, leaving approximately 25 to 30% of patients with rheumatoid spondylitis showing permanent peripheral involvement, most commonly of the hips and shoulders. Ocular involvement including iritis, uveitis, and iridocyclitis may occur, usually in recurring attacks; blindness may ensue from these.

Laboratory Tests.—The only laboratory procedure which is of value in the diagnosis of rheumatoid spondylitis is roentgenologic examination. Even this may be entirely noncontributory until after the patient has had symptoms of the disease for from several months to one or two years. The earliest changes are those of sclerosis in the margins of the sacroiliac articulations, followed by a haziness in which the joint loses definition when viewed in the anteroposterior projection. Complete obliteration of the sacroiliac joints may occur late in the disease. As the disease progresses, sclerosis, narrowing, and obliteration of the apophysial joints occurs, and osteoporosis of the entire spine of varying degrees is noted. Ossification of the marginal portions of the annulus fibrosus, giving the appearance known as "bamboo spine," is a late but characteristic change.

TABLE 4.—*Significant Differences Between Rheumatoid Arthritis and Ankylosing Spondylitis*

	Rheumatoid Arthritis	Ankylosing Spondylitis
Sex ratio, males to females	1:4	10:1
Onset after age of 50 years	Frequent	Rare
Results of serologic tests for rheumatoid arthritis	+	−
Ocular manifestations	Rare	Common
Subcutaneous nodules	15%	Not present
Cardiac involvement, if present	Mitral valve, rare	Aortic valve
Therapeutic response to gold	+	−
Response to roentgenologic therapy	−	+
Ossification of annulus fibrosus	No comparable change	+

The sedimentation rate and C-reactive protein level may be elevated during acute exacerbations, but do not consistently parallel the activity of the disease as measured by progression of spinal stiffening. The serologic tests give negative results.

Diagnosis.—In its early stages ankylosing spondylitis of insidious onset may be confused with lumbago or low back strain. Spinal rigidity noted on attempted forward bending usually suggests a true arthritis, but a presumptive diagnosis only may be possible prior to positive roentgenologic findings. In cases of more fulminating onset with sciatic pain the differential diagnosis from a ruptured intervertebral disk may be a problem. Careful examination while the patient is in the prone position will usually reveal tenderness over the sacroiliac joints in arthritis and over the disk when this is ruptured. If spondylitis starts in the thoracic or cervical spine, the initial complaint may be referred to a viscus and may cause confusion with coronary artery disease or cholecystitis. The absence of other signs of visceral disease and the localization of tenderness in the spine usually clarify the problem.

Although involvement of the apophysial articulations of the cervical spine may be seen as a late manifestation of peripheral rheumatoid arthritis, the characteristic "bamboo spine" and sacroiliac involvement of ankylosing spondylitis are not seen. Neoplasms and tuberculosis of the spine may cause difficulty in the early stages. The sharp localization of these conditions and the severe pain accompanying malignancies usually suggest the differentiation —which is proved by roentgenologic examination.

Treatment.—No specific therapeutic modality exists. Therefore, the most important single fact the patient must learn is that this disease cannot be cured and that his future mobility depends on diligent attention to general rules of health and strict observance of daily periods of properly graded exercises. These are designed to maintain motions in the spine, preserve thoracic expansion, and promote proper weight-bearing alignment. Exercises should be preceded by a period of local application of heat to enhance circulation.

In general, mechanical supports are to be avoided. However, they may be of use in some patients with spondylitis who must continue work requiring long periods of continuous standing or sitting. During acute exacerbations and in cases of fulminating onset, bed rest is desirable. There, proper posture must be maintained, with the mattress firm and pillows avoided. Moist compresses or steam packs may be helpful in alleviating pain. As in other rheumatic diseases, salicylates are of value in relieving pain and may be employed to full therapeutic doses.

Roentgenologic therapy is often of value in controlling the acute symptoms of pain and stiffness during exacerbations. There is, however, accumulating evidence to indicate that patients so treated may be susceptible to leukemia in later life. In young girls menstrual abnormalities, including sterility, may be produced. Roentgenologic therapy should therefore be used with caution. Although its use in severe cases may be justified, the lowest possible dose should be employed.

Phenylbutazone therapy has proved its usefulness in this disease in both the acute and the chronic stage; however, because of the possibility of complications it, too, must be carefully controlled. Steroid therapy would seem to have less usefulness than it does in peripheral rheumatoid arthritis but may in some instances be of value in relieving acute exacerbations.

Summary.—As noted earlier in this section ankylosing spondylitis, although currently classified under rheumatoid arthritis, demonstrates significant differences from that disease. These are summarized in table 4.

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SIMPLE OR RADICAL MASTECTOMY?—Since even in the most skillful hands the conventional radical mastectomy may cause disfigurement, dysfunction and considerable psychic morbidity, it is extremely important to determine whether it is necessary to employ it routinely or to employ it at all. To date there is no proof that the results of radical mastectomy are better than those of simple mastectomy. Pathologists may theorize on the rationale of eradicating cancer by extended surgery, but in the final analysis it is the survival of patients that counts. . . . Today, many surgeons . . . know that radical mastectomy is not the operation of choice for cancer of the breast. . . . The lymphatic drainage of the breast is so rich and replete with plexuses that the direction of spread of malignant cells through these channels is understandably unpredictable and fortuitous. Drainage is generally toward the skin surface where a subcutaneous plexus of lymphatic vessels permits the cells to be carried in almost any direction. The cells may migrate medially to the internal mammary nodes, laterally to the axillary nodes, or even to the inguinal nodes. These migrations may require months or years. Periods of quiescence are followed by fresh migrations. . . . Paths of dissemination are never predictable. The lesion can spread to the supraclavicular nodes without involving the axilla; it may spread directly into the internal mammary group and mediastinum without involving the axilla; it can extend directly into the chest, over to the other breast and axilla, into the abdomen, and even down into the inguinal nodes. . . . Unless all these possible areas for dissemination of the disease are eradicated, any procedure may be doomed to failure. . . . Proliferation along lymph channels is not the only method of dissemination. What is even more treacherous, is the spread of the disease by venous channels. . . . Surgery is the best modality of therapy for operable cancer of the breast, and simple mastectomy with postoperative radiation is to be preferred to radical mastectomy.—T. C. Case, M.D., Simple Surgical Therapy for Operable Carcinoma of the Mammary Gland, *Journal of the American Geriatrics Society*, May, 1959.

COUNCIL ON FOODS AND NUTRITION

Introduction

The Council on Foods and Nutrition has invited one of the leading authorities in the field of radiation biology to present a brief report on radioactive residues in foods. As more data are becoming available all the time, follow-up reports on the various aspects of the problem will be published in this column to keep physicians informed of current developments. The Council has authorized publication of the following report.

PHILIP L. WHITE, Sc.D., *Secretary.*

RADIOACTIVITY IN FOODS

Cyril L. Comar, Ph.D., Ithaca, N. Y.

There is little doubt that atomic energy will assume an important role in our civilization, and it is appropriate that future possible hazards should be evaluated. At the present time, it can be concluded that there is no reason for any change in our nutritional habits or food technology as a result of fall-out contamination. Research must continue, however, so that recommendations can be made to minimize the intake of radioactive contamination should this ever become necessary.

Although environmental contamination now existing is due almost entirely to fall-out from nuclear weapons, peacetime operations may become increasingly important as sources of radioactive contamination. In addition to fall-out, small quantities of radioactive materials may be released into the environment as a result of such operations as mining of uranium and thorium ore and fuel processing; reactor installations in power plants, submarines, ships, and aircraft (normal operations and accidents); and radioisotope applications in medicine, industry, and agriculture.

Determining Factors in Hazard of Radioisotopes

The relative hazard of radioactive materials will be governed by the amount released into the environment, physical half life, efficiency of transfer through the food chain to the human diet, degree of absorption by the body, and length of time retained in the body. By these criteria, the radioisotopes from fall-out of the greatest concern are iodine, barium, strontium, and cesium. Extensive data are available on the passage of these radioactive materials through food chains and subsequent implications.[1] Table 1 summarizes their characteristics from the standpoint of environmental contamination.

The radioisotopes of iodine collect in the thyroid gland and those of barium concentrate in bone. Since isotopes of both of these elements have short physical half lives, they can be dangerous only during certain periods, depending on the frequency and the nature of production of contamination. Experience has indicated that iodine-131 transmitted in milk may be important at short times after releases such as in reactor accidents. Strontium-89, which is produced in higher activities than strontium-90, may be more hazardous shortly after production, while strontium-90, with a much longer half life, becomes more dominant with time. The strontium radioisotopes, of course, are cumulative in bone. Cesium-137, which follows potassium in metabolism, is considered less of a hazard than strontium-90 because it is turned over relatively rapidly in the body, it is not selectively concentrated in any one part of the body, and it does not pass appreciably from soil to plant in the food chain.

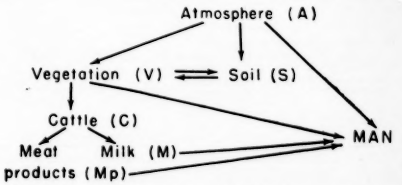

Diagram of main terrestrial food chains by means of which environmental radioactive contaminants reach the human population.

Radioactive contaminants are transferred to man by means of specific pathways through the main terrestrial food chains. These food chains are illustrated diagrammatically in the figure and the primary pathways of barium, iodine, strontium, and cesium are shown in table 1. As an example, strontium-90 is deposited from the atmosphere on the foliage of plants and on the soil. Transfer between soil and plant proceeds in both directions by normal root uptake and by washing from leaves or death

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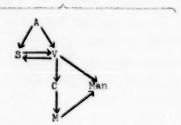
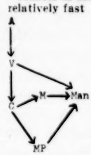
of leaves. Strontium-90 reaches the human body by direct consumption of vegetation and of milk from animals that have fed on the vegetation.

The relative importance of the various pathways depends on many factors, for example, the composition of the soil (calcium level) and the nature of plant cover. A heavy root mat will tend to trap fall-out strontium and delay its reaching the soil for dilution with soil calcium, while at the same time permitting absorption into the plant from the base of the stem. The agricultural management of crops and livestock, which includes the plowing depth, fertilizer practice, and type of feeding (barn or pasture) employed, is another factor to be considered. Also of great importance are dietary habits of the population and food technology. As an illustration, in the processing of frozen vegetables, washing them prior to freezing will remove some of the surface contamination. If nuclear tests are stopped, the soil reservoir will become increasingly important; therefore, the time pattern of contamination has to be taken into account. Although food-chain considerations are extremely complex, certain generalizations can be made. It is obvious that the pathways that require considerable time in passage to man (for example, via the soil) are of no significance for the short-lived radioisotopes,[2] iodine-131 and barium-140. It also appears that the present contamination of diets originates mainly from surface contamination rather than from the soil reservoir.

The movement of strontium radioisotopes from soil to man is interrelated and, to some extent, governed by the simultaneous movement of calcium. In all steps of the food chain from vegetation to human bone, calcium is preferentially utilized relative to strontium. Thus, it has been calculated that at equilibrium the strontium-calcium ratio in bones of young infants would be from 3 to 12% of that in vegetation, with values of 8 to 16% in the bones of persons over 6 months of age. Although milk is our primary source of calcium, the discrimination against strontium relative to calcium in passage from the feed of the cow to its milk tends to reduce the importance of milk as a source of strontium-90. While dairy products furnish some 80% of our dietary calcium, they may supply somewhat less than 40% of the total strontium-90 intake when steady-state conditions are established. Attention should also be given to contaminated water supplies as a possible source of strontium-90. In making estimations, the entire strontium-90 and calcium intake of the population must be considered.

The soil reservoir probably will not be an important factor for cesium-137 because of the fixation of this element in the soil and its consequent unavailability to the plant. At the present time, about 60% of the cesium-137 content of the average diet is derived from dairy products, 25% from meat products, and the remainder from vegetables, cereals, and fruits.

TABLE 1.—*Comparison of Radioisotopes in Environmental Contamination*

	Iodine-131	Barium-140	Strontium-89	Strontium-90	Cesium-137
Physical half life	8 days	13 days	51 days	28 years	30 years
Metabolic behavior	collects in thyroid	like calcium, collects in bone	like calcium, collects in bone	like calcium, collects in bone	like potassium, collects in muscle
Removal rate from body	fast	slow	slow	slow	relatively fast
Main pathways in food chain*					
Samples for monitoring radioisotope levels	vegetation, milk, and thyroid	vegetation and milk	soil, vegetation, milk dairy products, bone, and aquatic food	soil, vegetation, milk dairy products, bone, and aquatic food	vegetation, milk, dairy products, meat, and whole body
Maximum permissible radioisotope concentrations, μμc per liter†	3,000	200,000	7,000	80	150,000
Radioisotopes in milk, μμc per liter‡	121	42	52	6.4	57
Comparative radiation dose to humans, rad	<0.04 to thyroid in 1955 and 1956	<10% of strontium-89 dose	approximately from 1 to 20% of strontium-90 dose	approximately 0.2 to 0.4 to skeleton over 70-yr. period from present tests§	approximately 0.001 per year from present levels

* A = atmosphere V = vegetation M = milk S = soil C = cattle MP = meat products.
† Recommended maximum permissible concentrations for specific radioisotopes in drinking water as derived from recommendations of National Committee on Radiation Protection and Measurements. These concentrations and milk values are quoted by Public Health Service.
‡ Levels found in United States from July, 1957, to July, 1958.
§ This estimation includes recent analytical data and concepts of nonuniform stratospheric inventories developed at May, 1959, congressional subcommittee hearings.

Radioisotope Levels

The present levels of these radioisotopes in the biosphere (soil-plants-animal products–man) can be determined with reasonable accuracy by radiochemical analysis. For purposes of illustration, table

1 presents some of the average radioisotope values for milk in the United States for the years 1957 and 1958. In the early part of 1959, values for strontium-90 in milk from various locations in the United States all averaged well under 30 micromicrocuries ($\mu\mu c$) per liter. These values are below the recommended maximum permissible limits for lifetime exposure to specific radioisotopes in water. Discussion of maximum permissible levels is beyond the scope of this paper. It is urged, however, that scientists and laymen should develop a clear understanding of what is implied by figures given as maximum permissible levels and how these figures are derived.[1]

Dietary levels of strontium-90, which are expressed as micromicrocuries of strontium-90 per gram of calcium, have been estimated at approximately 0.4, 2, 4, 5, and 7 for each year from 1953 to 1957 respectively. It is estimated that the maximum levels from tests to date will occur from 1962 to 1965 and that the average maximum level in the diet of persons living in the United States at that time may reach about 24 $\mu\mu c$ of strontium-90 per gram of calcium. Recent considerations indicate that much of the present strontium-90 in milk may not have come through the soil but found its way into the plant by foliar absorption or other processes. This has important implications: (*a*) if there is no further testing, the levels may fall fairly rapidly, (*b*) the contamination of food when only the soil route is operative should be much lower than at present, and (*c*) this would explain why levels in non-milk foods are not greatly lower than in milk foods as is expected because of the dairy cow's preferential use of calcium.

Milk from numerous areas has been analyzed to determine the local variation in dietary levels of strontium-90. The highest values observed were about five times the mean value, while milk from cows fed on vegetation grown in low-calcium soils were approximately twice the mean value. There appears to be less variation in the levels found in the human population, presumably because the individual consumes food that originates from many areas. It is not yet possible, however, to express variability in precise statistical terms.

The most direct and important evidence comes from analysis of tissue samples from the human population. Typical values, calculated and expressed in terms of radiation dosage rather than concentration of radioisotopes, are given in table 1. A scale of values to indicate expected response of man to radiation is presented in table 2. It can be noted that present and anticipated levels of radioactivity in man, based on the effects of nuclear tests to date, are below those known to produce any observable effects. However, indiscriminate testing of nuclear weapons, either by many nations or at higher rates, could lead to levels of strontium-90 in the food chain that would be of definite concern. The most difficult issue, particularly because of its moral overtones, is whether present levels (also of carbon-14)[3] will produce absolutely no incidence or will produce only finite incidences of genetic or somatic harm in the world population. This is a complex and controversial matter relating to linearity of response and patterns of threshold versus nonthreshold behavior at low levels.

Low-level monitoring, which detects excess radiation before health hazard levels are reached, will become important as a public health function to give advance warning of any peacetime operational difficulties. Public reassurance will be provided by monitoring at natural radiation levels before and after nuclear installations are placed in operation.

TABLE 2.—*Effects of Radiation on Man*

Radiation Dose, rad	Source and Conditions	Observations
3,000-6,000	3.6 μc radium or x-radiation to skeleton	Bone sarcoma
300	0.4 μc radium	Minimal nondeleterious bone changes
90	0.1 μc radium	No observable effects
50-60	(suggested as levels that would double leukemia incidence)	
7-15	Natural background	No observable effects
10	(recommended upper limit of radiation from any man-made source)	
0.2-0.4	(estimated dosage from strontium-90 from tests to time of writing)	
0.05	(estimated dosage from cesium-137 from tests to time of writing)	

Summary

Although at the present time there is no indication for a change in our dietary habits, broad-scale research on the problem of radioactivity in foods and its implications must continue for future public welfare. Even if testing of nuclear weapons is halted, peacetime applications of atomic energy will release some radioactive materials into the environment. Therefore, close supervision of the dietary levels of radioisotopes and understanding of possible effects on man are necessary for evaluation of atomic energy benefits versus biological cost.

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HARRIS'S MIGRAINE OR CLUSTER HEADACHES

MIGRAINE is a fascinating disorder, kaleidoscopic in its manifestations and instructive in the leads it affords about function of the brain and about behavior. Despite a statistical relation between migraine and epilepsy, the sufferer of migraine has within him something that powerfully resists the spread of the abnormal electrical discharge. Otherwise why does he not have convulsions, when he is subject to all sorts of other jacksonian phenomena. Perhaps the abnormal electrical activity during the prodromata of migraine is essentially cortical and does not spread far from its original focus. Attacks that produce involuntary movement of a skeletal muscle are rare; weakness or inefficiency occur to be sure—and numbness, dysphasia, and of course the marvelous spectrum of scintillating scotomata.

A variant of the galaxy that is migraine was recently reported by Bickerstaff [1] under the heading "The periodic migrainous neuralgia of Wilfred Harris." This condition [2] was first systematically described by Harris in 1926. A decade later when he termed it ciliary neuralgia, Harris weakened his original title and sent many practitioners on a trek through the sinuses and nerve plexuses with probe and scalpel. This type of headache has been known also by Horton's [3] term, histaminic cephalalgia. The groups at Duke [4] and at the Montefiore Hospital in New York [5] have called it "cluster headache," because of the curious tendency of attacks to occur in clusters between periods of freedom.

Despite the fact that the syndrome is rarely recognized when first seen, it is characteristic. The patient is more often a man than a woman (between two and four to one) and between the ages of 30 and 50 years. Bickerstaff reported a case in a patient 11 years old at onset, the youngest on record. Another writer has observed a patient aged 64 who had his first attack at the age of 59.

The attacks of pain are intolerable. Fortunately their duration is relatively short, minutes to an hour; although an attack may continue for several hours. The constant boring or throbbing pain is located lateral to an eye a few centimeters behind and above the outer canthus. It may spread to involve the remainder of the cheek, the forehead, the temporal scalp, and rarely the neck. The pain usually affects the same side repeatedly, in fact the same spot. In contrast to the more usual migraine where the patient prefers to recline and pull the covers over his head, with Harris's migraine he cannot recline and usually must pace. There seems to be a relationship between the pain and the muscular activity that it occasions. There is congestion of the conjunctiva on the same side as the pain and sometimes stuffiness of the ipsilateral nostril. Flushing of the ipsilateral forehead and cheek have been seen occasionally. Vomiting practically never occurs. Some patients believe they may precipitate attacks in the same manner as do persons with trigeminal neuralgia, by chewing, washing their face, or brushing their teeth. Between attacks these people are well.

The attacks tend to occur at the same time of day or night. Characteristic is the pain that arouses a majority of these patients between 2 and 3 a. m. A bout usually lasts for weeks, during which the patient has at least one attack daily. He may have them every two hours or so, or the attack may become a "status migrainous," when he is rarely free of pain.

The bouts recur irregularly and then may cease after occurring for years. Ten of Bickerstaff's 30 patients had had attacks for over 10 years, two had them for 30 years.

Most of these patients have previously had a more classic form of migraine, which is replaced by the Harris form. In Bickerstaff's 11-year-old child the attacks of pain ceased spontaneously after two

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years and were replaced by ordinary migraine at the age of 16. Many patients give a history of migraine in near relatives.

Sir Charles Symonds [6] has devised a successful symptomatic treatment for Harris's migraine with regular prophylactic injections of ergotamine tartrate. The patient is taught to give himself intramuscular injections of ergotamine tartrate, 0.25 mg. three times a day, for five days in each week. The two free days allow the patient to determine whether the bout of pain has ceased. An occasional patient will require 0.5 mg. with each injection to obtain relief. While some patients vomit after early injections, this will cease after a few days without alteration of dosage. With this drug some patients are relieved of the Harris type of migraine but attacks of ordinary migraine then return. Ergotamine tartrate injections should be discontinued gradually rather than abruptly. Occasionally sudden withdrawal of the drug is accompanied by generalized headache. The usual precautions pertain about using these amounts of a potent vasoconstrictor substance.

There has been general agreement among neurologists that this type of head pain is a variant of migraine. The involvement is primarily if not exclusively of branches of the external carotid artery which dilate in a precipitate fashion. These patients cannot tolerate alcoholic drinks during periods when headaches are recurring, presumably because of their vasodilatory effect. Both Harold Wolff and Kunkle and their co-workers have been searching for the substance(s) released at the site of the pain in some forms of migraine. Some patients believe that, whatever it is, it may be "drawn off" or "drained away" by muscular activity.

Patients having Harris's migraine seem to have personality patterns comparable to those in patients with other types of migraine. Since there seems to be a great preponderance of patients having right-sided attacks, the problem might in some way be associated with handedness and eyedness. Right and left sidedness and its relation to personality is a fascinating study, as shown in Blau's [7] excellent monograph, "The Master Hand."

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ORGANIZATION SECTION

ANNUAL CONFERENCE OF MENTAL HEALTH REPRESENTATIVES

On Nov. 20-21, 1959, the Council on Mental Health will hold its Sixth Annual Conference of Mental Health Representatives of State Medical Associations at the Drake Hotel in Chicago. The general theme of the conference, "Organized Medicine in Its Relationship to the Hospitalized Psychiatric Patient," will be divided into six group discussion areas: (1) in the state hospitals and other public mental hospitals area, (2) in the private mental hospitals area, (3) in the general hospitals area (psychiatric services in general hospitals), (4) in the outpatient psychiatric clinics area, (5) general rehabilitation services area, and (6) area of medicolegal aspects of commitment, discharge, and other court procedures relating to the mentally ill.

For the first time the Council will invite the commissioners of mental health of the 50 states to attend this year's conference. The Council feels the participation of the commissioners, along with the chairmen of the state association mental health committees, will make conference discussions and decisions, with respect to improvements that can be made in the care and treatment of the mental patient, much more effective.

The Council also intends to encourage subsequent meetings on this general theme at state levels to be organized and led by the state chairmen and commissioners jointly after the November conference.

Dr. John D. Porterfield, deputy surgeon general, U. S. Public Health Service, will be the guest speaker at the dinner meeting, Friday, Nov. 20.

BEQUEST TO RESEARCH FOUNDATION

The American Medical Research Foundation has received $12,274.71 from the estate of Miss Katherine Zimmerman of Monroe, Mich. C. Joseph Stetler, head of the A. M. A.'s law division, said the foundation may receive about $3,000 more if money held for taxes is not used by the estate. Miss Zimmerman, who died June 19, 1958, left 20% of the residue of her estate to the A. M. R. F.

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THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

Most American physicians probably never have attended a state or national medical meeting at which there were no scientific exhibits, no scientific program, and no commercial displays. Recently I attended such a session, the second congress of the Brazil Medical Association held in the bustling city of over 600,000.

Despite the lack of scientific activities, approximately 500 Brazilian physicians, or 5% of the 10,000 membership, attended the meeting of the seven-year-old Brazilian Medical Association. For days—and nights—these physicians worked on socioeconomic problems in workshop conferences and in the House of Delegates.

I was invited to speak to the Brazilian physicians on the subject of the private practice system of medicine, free enterprise, voluntary health insurance, and the scope of government medicine in the United States. I was given an entire morning on the program. After my hour-long address, in which I explained, defended, and promoted our American system, I was asked scores of questions.

On the previous day the deputy minister of health of Great Britain was allotted the morning session to outline the British national health plan and to answer questions.

The two of us were the featured foreign speakers, and I assure you that we tangled verbally but amicably many times over the merits of our respective systems.

I believe that the young Brazil Medical Association and its member-physicians have great potential. With the freedom to function as an association of private practitioners and with the freedom to practice personal medicine as individual physicians, the association and doctors can bring the best medicine to the most people in Brazil. Of course, their challenges and opportunities are many, but having witnessed the physicians' dedication to work, I see no reason why the quantity and quality of medical progress there cannot be rapid and all-encompassing.

Already many Brazil hospitals are excellently equipped. The surgery I saw performed was as good as any I have seen in the United States. And Brazil has hundreds of well-trained physicians in all the specialties and in general practice.

As I saw it, however, Brazil's public health and sanitation facilities must be improved if many of the communicable diseases are to be prevented. For example, it is necessary to drink bottled water in all cities. Tropical diseases, too, are widespread and they are not being brought under control as rapidly as they probably could be.

The nation also has a medical school problem. While there are fine institutions in the country, there are many, many diploma mills in operation. These have arisen because there is no licensure of physicians.

Physicians of Brazil have expressed to me their desire of closer association with American medicine, and I hope that we can cooperate with them in solving some of the same health and medical education problems that we have had to deal with. They also would like to send more of their people here for training. This too I hope can be done in the interests of improved medicine and medical care in Brazil and in our Western Hemisphere. My experience in Brazil has warned me that if we do not offer our assistance, others certainly will.

Louis M. Orr, M.D.
Orlando, Fla.

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COUNCIL ON NATIONAL DEFENSE

REGIONAL CD CONFERENCE

The central theme of the fifth regional meeting of the A. M. A. Committee on Disaster Medical Care was the heightened interest evident in preparedness for disaster when natural or industrial disaster, rather than the enemy inflicted nuclear holocaust, is emphasized. The Committee met in San Francisco on Sept. 26, 1959, with representatives of the medical societies of California, Nevada, and Utah of OCDM Region 7 and of Idaho, Oregon, and Washington which are in OCDM Region 8.

As at the four prior regional meetings of the Committee, the state reports on the status of medical preparedness for disaster ranged widely from that of California where planning, programming, and funding have resulted in a high degree of capability to Oregon with its funding and other problems and Idaho where the general lack of interest was recently dispelled somewhat by the Yellowstone National Park earthquake. It was agreed that the local disaster is the best stimulant to interest in medical as well as general public preparedness for disaster. A fire in Nevada in 1957 and a recent explosion in Oregon greatly stimulated disaster medical care activity as did the earthquake in Idaho. California has long emphasized preparation for natural disaster.

Prior regional meetings of the Committee on Disaster Medical Care of the Council on National Defense were held in Atlanta, Dallas, Boston, and Colorado Springs. The next meeting will be held in Chicago on Jan. 23, 1960.

COUNTY MEDICAL SOCIETIES CIVIL DEFENSE CONFERENCE

Medical and health personnel will be acquainted with some of the vital activities that local physicians and individual groups are doing in the field of medical preparedness for disaster at the conference at the Morrison Hotel in Chicago on Nov. 7-8, 1959.

Two reports at the conference will evaluate the hospital and medical disaster programs in operation during the school fire at Our Lady of the Angels' school in Chicago on Dec. 1, 1958, and the tornado which hit St. Louis this year. Top medical authorities will also report on preparedness and participation in civil defense programs in the federal government and at the state and local level. In addition, on Saturday afternoon, at workshop sessions, the conferees will discuss specific civil defense medical and health topics.

Highlights of the program will be talks by Congressman Melvin Price on the environmental and biological effects of nuclear attack, and by Major General Marshall Stubbs, chief chemical officer of the Army, on what everyone should know about chemical and biological warfare.

The registration fee of $10 includes two luncheons. Those planning to attend the conference are urged to register in advance by notifying the Council on National Defense, which annually sponsors this conference.

SAN ANTONIO'S MISSILE AGE HOSPITAL

The Office of Civil and Defense Mobilization has agreed to provide $300,000 for a nuclear survival complex to be built under the proposed $20,000,000 Southwest Texas Methodist Hospital at San Antonio. As reported in the April 1959 issue of the *Review*, the hospital will have in addition to its five stories above ground two floors below ground which will be constructed of reinforced concrete and will be designed to withstand any disaster. The hospital also will have its own power plant, underground water wells, and food stocks. In an emergency, the upper floors could be vacated and the hospital could operate for 30 days without access to the outside world. Other advanced features include a helioport where emergency patients can be flown by helicopter service; a closed-circuit TV system which will keep the nurse in contact with each patient; tele-thermometers capable of taking the patient's temperature from a distance; an electron beam generator which will disinfect virtually everything touched by human hands; and radar ranges to cook a full course meal by microwaves in 45 seconds.

REGIONAL CD UNDERGROUND CENTER

The First Session of the 86th Congress provided $2,400,000 to finance construction of a regional civil defense underground center at Denton, Texas. In the event of enemy attack, the center will insure decentralized federal guidance for Office of Civil and Defense Mobilization Region 5 which includes Texas, New Mexico, Oklahoma, Arkansas, and Louisiana. The facilities will also serve as an alternate National Control Center for civil defense should the OCDM establishments at Washington, D. C., and Battle Creek, Mich., be destroyed. The center will have a high degree of protection against blast and will be completely self-contained and permit sustained operations under adverse conditions of radioactive fall-out as well as chemical or biological warfare agents. The structure is planned to serve as a prototype for other regional defense headquarters.

DEPARTMENT OF ECONOMIC RESEARCH

SOME OBSERVATIONS ON FINANCIAL ASSETS OF THE AGED AND FORAND-TYPE LEGISLATION

Arthur Kemp, Ph.D., Leonard W. Martin, Ph.D.
and
Cynthia Harkness, B.A., Chicago

The famous British economist, Alfred Marshall, wrote many years ago: "Experience in controversies . . . brings out the impossibility of learning anything from facts till they are examined and interpreted by reason; and teaches that the most reckless and treacherous of all theorists is he who professes to let facts and figures speak for themselves. . . ."[1] The wisdom of this observation is forcefully brought home by an examination of the literature surrounding the report of the Department of Health, Education, and Welfare to the Committee on Ways and Means concerning hospitalization payments for beneficiaries of old age, survivors, and disability insurance (OASDI) and by the hearings conducted in July, 1959, by that committee on H. R. 4700 introduced by Rep. Aime J. Forand (D.) of Rhode Island. A striking feature of both the report and the testimony favoring the bill is the bias resulting from an almost complete lack of consideration of the assets of persons aged 65 and over and the almost exclusive emphasis on their cash income position.

Income—One of Many Measures

Even a cursory consideration of the problem should convince the reader that emphasis on money income tends to obscure the fact that many people aged 65 are at last reaching the time when they can retire on their savings. Why should it be difficult to understand that persons over 65 years of age, who have retired, have a lower income than those under 65 years of age who are still working and have not retired? Indeed, in a fairly prosperous society not devastated by inflation, one would expect a large proportion of those over 65 years of age and retired to be more comfortably off than those still at work.

Repeated again and again is the statement that about three-fifths of all persons 65 years or older had less than $1,000 money income in 1958. This statistic is presented in an article on money income distribution of the aged prepared by Lenore A. Epstein of the division of program research, Office of the Commissioner, Social Security Administration, which appeared in the June, 1959, issue of the *Social Security Bulletin*. Precisely the same statement was made by Wilbur J. Cohen before the Senate subcommittee on problems of the aged on June 16, 1959, and by Katherine Ellickson, assistant director of the Social Security Department of the AFL-CIO, as author of a bulletin issued June 23, 1959. On the same day Dr. Basil C. MacLean, president of the Blue Cross Association, stated in virtually the same words the same statistic at the University of Michigan's 12th Annual Conference on the Aging at Ann Arbor, Mich. Whether or not the source of these statements was the report of the Secretary of Health, Education, and Welfare to the Committee on Ways and Means one cannot say, but the statement does appear in the report dated April 3, 1959, on page 8: "Thus, both in 1956 and 1957 three-fifths of all people 65 and over had less than $1,000 in money income. . . ."[2]

Let us accept this statistic as a fact. Indeed, those who repeat it appear to accept it without question and to consider that it speaks for itself. This statistic, combined with the assumption that income is a sufficient measure of financial status, implies that the aged as a group suffer from poverty and privation because of their low incomes in a generally prosperous society. The implication can be questioned if one points out an equally accurate statistic, namely, that in 1957 almost one-half of all persons over 14 years of age also had incomes of $1,000 or less per year. Looking further one finds that 47% of all persons between the ages of 14 and 65 had incomes of $1,000 or less per year in 1957.[3] Yet, it also is true that the median family income in 1957 was approximately $5,000 per year.

Misleading Arrangement of Data

Can all these things be true? Can there be a median family income of $5,000 per family while almost one-half of all persons earn $1,000 or less per year? The answer is yes. Both statements are true, and after a very little reflection it is not surprising that one can obtain such a high percentage of those aged 65 or over who have incomes of $1,000 a year or less, or even that one can obtain such a high percentage of all persons over the age of 14 years with such incomes. Parenthetically, of course, one would not be surprised to find the incomes of those under 14 years of age exceptionally low indeed, and for much the same reason.

Director (Dr. Kemp), Assistant Director (Dr. Martin), and Research Assistant (Miss Harkness), Economic Research Department, American Medical Association.

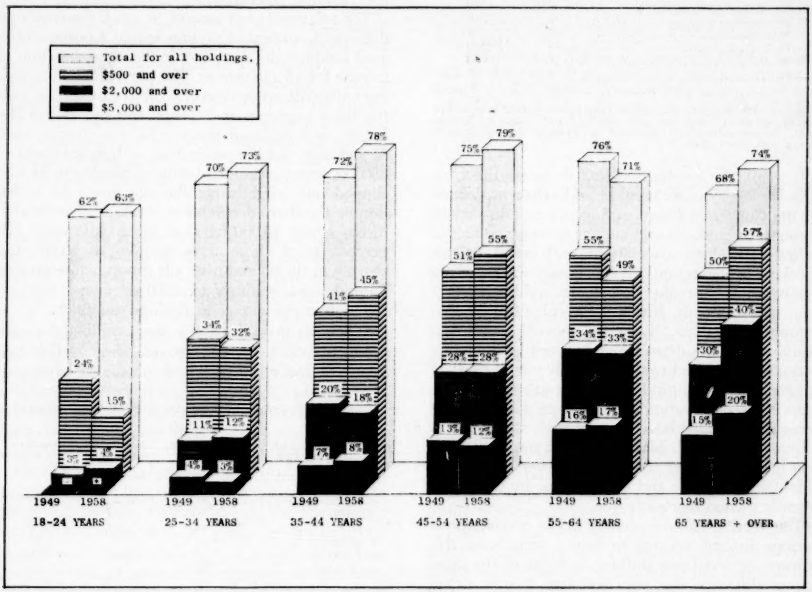
The important fact to be remembered is that the money income figures cited by the Department of Health, Education, and Welfare and others refer to individual and not to family income. In other words, let us imagine that a club is composed of a number of persons and their respective husbands or wives and that the conditions of membership in the club are (1) that only one member of each family be an income earner and (2) that the average income per family be in excess of $20,000 per year. This is the club. By using the same statistical technique or formulation as that employed by the Department of Health, Education, and Welfare, one-half (50%) of the members of that club have incomes of less than $1,000 per year (zero incomes, in fact) and, so long as the same conditions exist, will continue to have zero incomes even though the average income per person for the club has to be, by the very conditions of membership, in excess of $10,000 a year.

All of this leads to the conclusion that money income of the aged population, arranged on a per capita basis, is an insufficient and misleading measure of financial status. An appropriate measure of the aged's financial status should include also nonmonetary income, assets, and other resources.

Growth in Assets of the Aged

An examination of the Federal Reserve Board's annual sample Survey of Consumer Finances reveals some interesting and supporting evidence concerning the aged's liquid assets and the rate at which those assets have been accumulating between 1949 and 1958. These are shown graphically in the figure. Between these two years, persons aged 65 and over accumulated liquid assets faster than any other age group. During this period the proportion of the aged group's ownership of liquid assets rose from 68 to 74%.[4] This means that in 1958 nearly three out of every four persons aged 65 or over owned liquid assets in some form. In contrast the percentage of persons 55 to 64 years of age who owned liquid assets dropped to 71% in 1958, while the average for all groups between the ages of 18 and 64 years rose from 71 to 73%.

The proportion of those aged over 65 who had liquid assets of $2,000 or more increased from 30% in 1949 to 40% in 1958; for liquid assets of $500 or more, the respective increase was from 50 to 57%. It should be noted that, generally speaking, the proportion of those over 65 years of age who have liquid assets of $500 or more, $2,000 or more, and



Percentage distribution of liquid asset holdings of spending units, by age of head of spending unit, 1949 and 1958. (Source: *Fed. Res. Bull.* 35:911 [Aug.] 1949; 44:1055 [Sept.] 1958.)

*No cases reported or less than ½ of 1%.

$5,000 or more is higher than for any other age group. The Federal Reserve Board's annual sample Survey of Consumer Finances also revealed that in 1958 the group aged 65 and over gained the highest median value in liquid asset holdings—$800 for all aged persons and $2,450 for the 74% holding liquid assets.[4a]

TABLE 1.—*Distribution of Liquid Asset Holdings and Incomes in Age Groups**

Age of Head of Spending Unit	Early 1958: Spending Units with Liquid Assets of More Than $500, %	Early 1958: Spending Units with Incomes of $3,000 or More, %
18 to 24	15	46
25 to 34	33	81
35 to 44	45	85
45 to 54	54	80
55 to 64	50	58
65 or over	56	27

* Source: The Financial Position of Consumers, Federal Reserve Bulletin 44:1052 (Sept.) 1958, and correspondence with James N. Morgan, Ph.D., Program Director, University of Michigan Survey Research Center, Ann Arbor, Mich.

It should be emphasized that these are the gross data for liquid assets only. Liquid assets, as defined by the Consumer Finances Survey, include savings accounts in banks, postal savings accounts, shares in savings and loan associations and credit unions, checking accounts, and savings bonds. Excluded are homes and other real estate, stocks, and bonds other than savings bonds. If it were possible to take into account ownership of equity securities and less liquid assets, the discrepancy in asset holdings between the aged and others probably would be even greater than the liquid asset data alone can illustrate. This observation follows from the fact that generally the aged have more of such assets than is commonly realized. Moreover, their net asset position is clearly better than that of others since their indebtedness is low and their homes are characteristically owned mortgage-free.

The aged are above average in the percentage of persons having savings in liquid form, and this percentage has been shifting in favor of the aged group although the younger age groups would normally be thought to have a greater earning power. In September, 1958, the *Federal Reserve Bulletin* concluded that "There was a marked tendency . . . for the frequency of large holdings—particularly of savings accounts or shares—to increase with age. One-half of the savings deposit holders who were 65 or older had $2,400 or more in this form, compared with a median of $720 for all holders."[5]

The Relation of Assets, Income, and Age

One normally expects to find a positive correlation between annual money income and the size of liquid asset holdings. But, here again, because the logical relationship is between liquid asset holdings and total money income earned over a lifetime rather than annually, the correlation cannot be expected to be as high for those in the age group over 65, a large proportion of whom have retired. Surely there is a relationship between savings and income; but more significant is the relationship of age to savings despite the relationship of age to income.

Table 1 provides distributions of both liquid asset holdings and incomes with respect to age and reveals most clearly that savings tend to rise almost continuously with age. The percentage of spending units with liquid assets of more than $500 early in 1958 rose with age except for the age group 55 to 64, which is reported to be an age group severely hit by the 1957-1958 recession.

The relationship of income to age is considerably different from that of savings to age. Consequently, asset holdings did not move in the same direction as income for all age groups. The percentage of spending units with an income of $3,000 or more rose over the three youngest age groups, fell slightly for the fourth, and declined sharply for the groups aged 55 and over. Yet the percentage with liquid assets of $500 or more continued to rise through age 54 and slipped only slightly for the age group 55 to 64, despite the sharp decline in percentage of units with incomes over $3,000 for that group. Moreover, the percentage of those with incomes of $3,000 fell sharply in the 65 and over age group, while savings (liquid asset holdings of $500 or more) reached the highest percentage in this age group.

When, as in table 2, the asset holding data are arranged within income groups, some further evidence of the relationship of income to savings is revealed. In every respect the percentage of spending units with any assets at all or of the specified sizes was greater when the income was greater—$3,000 to $5,000 as compared with those of $3,000 or less. However, with rare exceptions the percentages of spending units with assets increased with the age of the head of the spending unit. The

TABLE 2.—*Relation Between Age, Income, and Savings**

Age of Head of Spending Unit	% Who Are Liquid Asset Holders	% with Liquid Assets of $500 or More	% with Liquid Assets of $2,000 or More
Spending Units with Incomes of $3,000 or Less, 1958			
18 to 24	51	5	†
25 to 34	34	16	3
35 to 44	45	23	5
45 to 54	46	26	12
55 to 64	51	26	16
65 or over	65	45	30
Spending Units with Incomes Between $3,000 and $5,000, 1958			
18 to 24	72	17	6
25 to 34	67	21	6
35 to 44	68	27	10
45 to 54	78	49	24
55 to 64	72	46	31
65 or over	90	81	57

* Source: Derived from table LAT 9, Study 666, for the Economic Behavior Program, University of Michigan Survey Research Center, Ann Arbor, Mich., 1958, unpublished data.
† Less than 0.5%.

exceptions occurred only in the 18 to 24 and 55 to 64 age groups. Evidently savings are not determined by income alone.

Indeed the size of the percentages for the group aged 65 and over is striking. While almost 75% of the aged had incomes of $3,000 or less (in 1957), nearly half of them in this income bracket owned liquid assets of $500 or more in 1958, and 30% had liquid assets valued over $2,000. Similarly the aged had the highest percentages among those with incomes ranging between $3,000 and $5,000. Eight of every 10 spending units in the age group 65 and over held assets of $500 or more and 57% had liquid holdings valued at $2,000 and above.

This does not mean, of course, that all persons over 65 years of age are rich and all those under 65 poor. It does suggest, however, that the problem of the aged is not simply one of age, or even one of money income and age. The problem is not a group problem; to the extent that it can be argued that some persons cannot afford medical care, the argument calls for either an extension of the deductible provision in income tax laws or, at most, for some subsidization of the poverty-stricken.

Conclusions

It should be apparent that the use of money income alone in assessing the financial status of those over 65 years of age may lead to erroneous conclusions. The relatively substantial liquid assets of those over 65 years of age are of great importance. These observations raise some questions as to the desirability, and even the sincerity, of legislative proposals designed to compel those under 65 years of age to pay for the medical care costs of those over 65, regardless of financial status. Certainly, in many individual cases those over 65 are better able to afford medical care than those under that age.

Physicians and others whose efforts are devoted to providing the best quality of medical care and to preserving and extending human life should not overlook the implications of programs drawn up by an alliance of "experts" with a vested interest in governmental activities and politicians seeking election or reelection. There are indeed chronic problems of aging and the aged, but, above all else, they are individual problems of individual human beings. Moreover, if governments will refrain from engaging in activities sure to destroy the purchasing power of people's accumulated dollars, the problem, at most, is temporary. Instituting a permanent program and a new bureaucracy to provide governmental health care for the aged, regardless of need, supplies a "cure" that may be worse than the "disease" in its ultimate effects on individual freedom and a free society.

Alfred Marshall, whose astute words were quoted above, raised the pertinent question more than a quarter century ago when he asked:

> Why should it be left for impetuous socialists and ignorant orators to cry aloud that none ought to be shut out by the want of material means from the opportunity of leading a life that is worthy of man? Of those who throw their whole souls into the discussion of this problem, the greater part put forth hastily conceived plans which would often increase the evils that they desire to remedy. . . .[5]

References

1. Memorials of Alfred Marshall, edited by A. C. Pigou, New York, Kelley and Millman, Inc., 1925 (reprinted 1956), p. 167.

2. Hospitalization Insurance for OASDI Beneficiaries, Report Submitted to the Committee on Ways and Means by the Secretary of Health, Education and Welfare in Compliance with House Report 2288, 85th Congress, April 3, 1959, p. 8.

3. Current Population Reports, Series P-60, no. 30, United States Department of Commerce, Bureau of the Census, (Dec.) 1958, p. 33.

4. (*a*) Financial Position of Consumers, Federal Reserve Bulletin 44:1055 (Sept.) 1958. (*b*) Financial Position of Consumers, ibid. 35:911 (Aug.) 1949.

5. Financial Position of Consumers, Federal Reserve Bulletin 44:1033 (Sept.) 1958.

6. Pigou,[1] p. 173.

GOVERNMENT SERVICES

NAVY

Navy Flight Surgeons.—If you have not been receiving your copy of *'Contact,'* the annual news magazine published by the Naval School of Aviation Medicine, please send your name and address to the editor, Capt. Philip B. Phillips, M. C., U. S. N., Naval Aviation Medical Center, Pensacola, Fla., so you may be put on the mailing list. The latest issue was distributed in October.

PUBLIC HEALTH SERVICE

Symposium on Venereal Diseases.—The Eleventh Annual Symposium on Recent Advances in the Study of Venereal Diseases will be held April 7 and 8, 1960, in the Palmer House, Chicago. The sessions will be open to all physicians and workers in allied fields who are interested in the venereal diseases. This symposium, sponsored jointly by the American Venereal Disease Association and the Public Health Service, will follow a venereal disease seminar for public health personnel which begins April 4. Anyone wishing to present a scientific paper on a subject related to venereal diseases should mail preliminary abstracts before Nov. 25 to Dr. William J. Brown, program committee chairman, in care of the Venereal Disease Branch, Communicable Disease Center, 50 Seventh St., N. E., Atlanta 23, Ga. Preliminary abstracts should give information sufficient to assist the program committee in making a decision as to their acceptance or rejection. Authors of accepted papers will be notified before Jan. 15. Final abstracts not exceeding 500 words will be required by March 1.

MEDICAL NEWS

ALASKA

Increase in Poliomyelitis.—Between Jan. 1 and Sept. 1, a total of 12 cases of poliomyelitis in Alaska were reported to the Alaska Division of Health. Only two cases were reported for the entire year of 1958. Seven of the 1959 cases were in Eskimos from the lower Kuskokwim River Area. Nine of the patients were infants 15 months to 3 years of age, two were children 7 and 9 years old, and one was a 47-year-old man. More than half of the cases were reported as paralytic, whereas the type of poliomyelitis was not stated for four and one was described as nonparalytic. In August a member of a group of 60 student tourists died of bulbar poliomyelitis at Whitehorse, Canada, en route from Fairbanks. After a temporary shortage of vaccine, the Division of Health supply was replenished in August.

CALIFORNIA

Annual Scientific Symposium.—The San Diego Academy of General Practice will hold its annual scientific symposium at the Hotel Riviera, Las Vegas, Nev., Nov. 12-14. Speakers on the program are as follows: Dr. Charles W. Mayo, Rochester, Minn.; Dr. William P. Thompson, Los Angeles; Dr. James E. M. Thomson, Lincoln, Neb.; and Dr. Robert E. Ryan, St. Louis, Mo. The banquet is planned for Nov. 12, 8 p. m. The symposium is approved for category I credit by the American Academy of General Practice. For information, write Dr. Harold P. Peterson, 5950 El Cajon Blvd., San Diego 15, Calif.

COLORADO

Open University Hospital Service.—The new Wardenburg Student Health Center, offering the University of Colorado Boulder campus its first hospital service in 33 years, opened Sept. 21. The million-dollar sandstone infirmary has a staff of 52 including physicians, nurses, and technicians. A gift from alumni Mr. and Mrs. F. A. Wardenburg, Wilmington, Del., it fills a gap in medical care that the university has felt since the medical school moved to Denver in 1925. Students, who previously obtained hospital care from downtown Boulder facilities, with costs partly paid through student health insurance, will have access to the new campus hospital facilities without additional cost. Serious illness and surgery will be treated at off-campus hospitals. The new building offers almost full hospital and clinical care.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

CONNECTICUT

Dr. Dublin Receives Health Medal.—Louis I. Dublin, Ph.D., Westport, is the 1959 recipient of the American Public Health Association's Sedgwick Memorial Medal "for distinguished service in public health." Dr. Dublin retired as second vice-president and statistician of the Metropolitan Life Insurance Company in 1952 after 43 years with the company, and since then has served as consultant to the Institute of Life Insurance on community health and welfare activities.

FLORIDA

Dr. Anderson Honored.—Dr. William A. D. Anderson, chairman, department of pathology, University of Miami School of Medicine, Coral Gables, received the annual award of the Scientific Products Foundation "for the most outstanding contribution to the improvement of laboratory techniques." The award was presented by the College of American Pathologists, of which Dr. Anderson is a past-president.

ILLINOIS

General Practice Meeting in Chicago.—The 12th annual scientific assembly of the Illinois Academy of General Practice will be held Nov. 9-12 at the Morrison Hotel, Chicago. The Congress of Delegates will meet Nov. 9 with Dr. Mladen Mijanovich, of Marengo, speaker, presiding. Dr. Robert E. Heerens, Rockford, president of the academy, will open the first scientific session with an address. Papers to be presented by out-of-state speakers include the following:

Heart Disease the World Over, Dr. Paul Dudley White, Boston.
Management of the Listless Patient, Dr. Paul E. Craig, Tulsa, Okla.
The Treatment of Insomnia by the General Practitioner, Dr. Leo H. Berman, Norwalk, Conn.
Common Sense Approach to Diagnosis of Fluid Imbalances, Dr. William D. Sniveley Jr., Evansville, Ind.
Mucolytic Agents in the Therapy of Respiratory Diseases, Dr. Meryl M. Fenton, Detroit.
Practical Considerations in the Prophylaxis of Rabies, Dr. Franklin B. Peck Jr., Indianapolis.
Carcinoma of the Thyroid; A Therapeutic Problem, Dr. John W. Cline, San Francisco.
Hormone Therapy in Early or Questionable Pregnancy, Dr. Harold A. Schwartz, Chattanooga, Tenn.
ACTH and Corticosteroids in Allergy, Dr. Stanley F. Hampton, St. Louis.

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Two panel discussions are planned: "Hospitals—the Privileges and Responsibilities of the Medical Staff Which Especially Concern the G. P." and "Steroids —When Are They Useful? Are They Harmful?" The annual dinner dance will be held Nov. 11, 7:30 p. m. Exhibits are planned. The program is acceptable for 10 hours category I credit. For information, write the Illinois Academy of General Practice, 14 E. Jackson Blvd., Chicago 4.

Chicago

Hospital Anniversary Program.—The medical staff of Mount Sinai Hospital celebrated the 40th anniversary of the hospital founding with a scientific program Oct. 30 in the Leopold Kling auditorium of the nurses' residence. The speakers were Dr. Ben W. Lichtenstein, president of the medical staff and attending neuropsychiatrist; Homer W. Smith, Sc.D., professor of physiology, New York University–Bellevue Medical Center. Dr. Lichtenstein presented "Multiple Sclerosis" and Dr. Smith, "Sodium: Five Hundred Million Years of Struggle with Too Little or Too Much."

Symposium on Cerebral Vascular Disease.—The Chicago Heart Association will present a symposium on cerebral vascular disease at the Knickerbocker Hotel, Saturday, Nov. 7, 2-5 p. m. Dr. J. C. Paterson, professor of medical research, University of Western Ontario, London, Canada, will serve as chairman of the program, which includes the following papers and speakers:

Cerebral Atherosclerosis—Histopathology, Pathogenesis, and By-Products, Dr. Matthew T. Moore, Philadelphia.
The Clinical Pattern in Certain Types of Occlusive Cerebral Vascular Disease, Dr. Clark H. Millikan, Rochester, Minn.
Recent Trends in the Therapy of Cerebral Vascular Disease, Dr. Sigmund N. Groch, New York City.

The following Chicago physicians will serve as discussants on the program: Drs. Orville T. Bailey, Wendel J. S. Krieg, Irving C. Sherman, Richard B. Richter, and Raymond A. Clasen. For information, write the Chicago Heart Association, 22 W. Madison St., Chicago 2.

Meeting to Discuss Internship.—A nationwide meeting on "The Future of the Internship" will be convened at Michael Reese Hospital and Medical Center, Saturday, Nov. 28. The special session, to which medical students, physicians, and educators have been invited, will take place in Rothschild Auditorium, 2816 Ellis Ave., from 9:30 a. m. to 12:45 p. m. Dr. Rachmiel Levine, director of medical education at Michael Reese, stated that "The program is an attempt to evaluate which type of postgraduate training is best suited to present-day medicine." The internship of the present and two views of its future will be discussed by Dr. E. Hugh Luckey, chairman, department of medicine, Cornell University Medical College, New York City, and Dr. Victor Johnson, Rochester, Minn., director of the Mayo Foundation for Medical Education and Research. "The Internship as It Appears to Today's Interns" will be reviewed by Dr. Richard H. Saunders Jr., Rochester, N. Y., director of the internship study, Association of American Medical Colleges. A panel discussion will complete the half-day session. The meeting is open to interested medical and educational personnel. It is sponsored by the administration of Michael Reese.

KANSAS

Dr. Frederickson Appointed Section Head.—The University of Kansas School of Medicine in Kansas City announced the appointment of Dr. Evan L. Frederickson to the staff as head of the section of anesthesiology and professor of surgery, effective Sept. 1. He was an assistant professor in anesthesiology in that section from 1953 to 1955. Dr. Frederickson comes to Kansas from the University of Washington, Seattle, where he was associate professor in pharmacology and anesthesiology.

MASSACHUSETTS

Dedicate Industrial Rehabilitation Unit.—The newly completed Industrial Rehabilitation Unit of the Boston University–Massachusetts Memorial Hospitals Medical Center, located on the seventh floor of Robinson Building at 750 Harrison Ave., was dedicated Oct. 1. The unit is headed by Dr. Henry J. Bakst, of Brookline, chief of the rehabilitation unit. It serves as a training facility for physicians, nurses, social workers, physical therapists, and medical students and provides care for patients with severe handicaps. The unit was formerly housed at Haynes Memorial Hospital.

MICHIGAN

Annual General Practice Meeting.—The 13th annual fall Postgraduate Clinic presented by the Michigan Academy of General Practice and the Wayne County Academy of General Practice will be held Nov. 11-12 at the Sheraton–Cadillac Hotel, Detroit. Dr. Clark W. Royer, Battle Creek, president of the Michigan academy, will preside at the first session. The program is arranged as a series of symposiums and panel discussions under the following titles:

Symposiums
- Modern Therapy
- Cardiovascular Disease
- Obstetrics
- Tranquilizers
- General Medicine

Panels
- Burn Therapy
- Corticosteroids in General Practice
- Newer Therapy

Scientific and technical exhibits are planned. The program includes 33 guest speakers. There is no registration fee, and academy members will be

allowed 11 hours category I credit for attendance. For information, write Dr. Francis P. Rhoades, 970 Maccabees Building, Detroit 2.

MINNESOTA

Lecture by New Zealand Surgeon.—Mr. Douglas Robb, senior thoracic surgeon to the Green Lane Hospital in Auckland, New Zealand, and prochancellor of the University of Auckland, delivered the 12th annual Judd–Plummer Memorial Lecture at the 37th annual meeting of the Alumni Association of the Mayo Foundation in Rochester. Mr. Robb presented "The New Zealand Medical Service: An Appraisal" on Oct. 9.

Name Executive Director for Medical Foundation.—Mr. Eivind Hoff Jr., Minneapolis, was named executive director of the Minnesota Medical Foundation, a nonprofit faculty-alumni-public group serving the Medical School at the University of Minnesota. The 1,200-member foundation, established in 1930, annually awards about two dozen scholarships to university medical students; raises funds for various programs supporting the school; and publishes a biweekly scientific journal, the *University of Minnesota Medical Bulletin*. Mr. Hoff, first full-time staff person in two decades of foundation history, was director of professional education and public relations for the Minnesota Heart Association since 1955.

NEVADA

State Medical Election.—The following is the result of election of officers of the Nevada State Medical Association at the annual meeting in Reno Aug. 22: Dr. Ernest W. Mack, Reno, president; Dr. Wesley W. Hall, Reno, president-elect; Dr. William A. O'Brien III, Reno, secretary-treasurer; Dr. Earl N. Hillstrom, Reno, alternate delegate to the A. M. A.; and Dr. Roland W. Stahr, Reno, immediate past-president. Dr. Hall will also serve as delegate to the A. M. A. House of Delegates.

NEW YORK

Graduate School of Psychiatry.—The New York State Department of Mental Hygiene opened a graduate school of psychiatry devoted to basic and advanced psychiatric education for its medical personnel on Sept. 14. Known as the New York School of Psychiatry, the school operates under a provisional charter granted by the board of regents of the University of the State of New York and offers a three-year training program. Prior to the completion of the organization of the school, the program was operated temporarily on a two-year basis. The new school serves the staffs of Brooklyn, Creedmoor, Kings Park, Pilgrim, and Central Islip state hospitals and Willowbrook State School. The graduate school is quartered in the medical-surgical building of Manhattan State Hospital on Ward's Island, where its teaching facilities include an outpatient clinic. Instruction includes a basic curriculum in psychiatry and advanced curriculums in specialized areas.

New York City

Dr. Meyer Honored.—The annual T. Duckett Jones Memorial Award, in the amount of $6,500, was presented to Dr. Karl Meyer, Columbia University College of Physicians and Surgeons, at the annual meeting of the Helen Hay Whitney Foundation research fellows and established investigators Sept. 26. This award was presented "in recognition of Dr. Meyer's pioneer and continuing work in the field of mucopolysaccharides." Dr. Meyer's work has included the first isolation of hyaluronic acid. Acquisition of new knowledge in the disease of connective tissues is the objective of the Helen Hay Whitney Foundation's program of support for "research fellows and established investigators of promise who desire an academic career as clinical investigators or scientists in the study of connective tissues and their diseases."

Personal.—Dr. Morris Schaeffer was named director of the Bureau of Laboratories of the City of New York Department of Health. Dr. Schaeffer comes from the Communicable Disease Center of the U. S. Public Health Service, Montgomery, Ala., where he served as medical director in charge of the Virus and Rickettsia Section.——Drs. John J. Kelly Jr. and J. Leonard Brandt resigned Aug. 31 as associate professors of medicine at the State University of New York Downstate Medical Center in Brooklyn. Dr. Kelly will become director of medical education at Mercy Hospital in San Diego, Calif., while Dr. Brandt has been named physician in chief of the Jewish General Hospital and director of medical research and lecturer in medicine at Magill University, Montreal.——Dr. J. Hamilton Crawford, clinical professor of medicine at the State University of New York Downstate Medical Center in Brooklyn, retired from active service on the faculty in August and was named clinical professor emeritus of medicine effective Sept. 1. Dr. Crawford has been a member of the faculty for over 30 years.——Dr. Charles L. Ravaris, Detroit, was appointed an assistant medical director of E. R. Squibb & Sons, Dr. Lawrence B. Hobson, medical director, announced.

NORTH CAROLINA

Campaign to Build Research Center.—Alumni of the Bowman Gray School of Medicine of Wake Forest College have set $500,000 as their goal in a campaign to build a new Research Center in Winston-Salem. Dr. George W. Paschal Jr., of Raleigh, is general chairman of the Research Center Fund.

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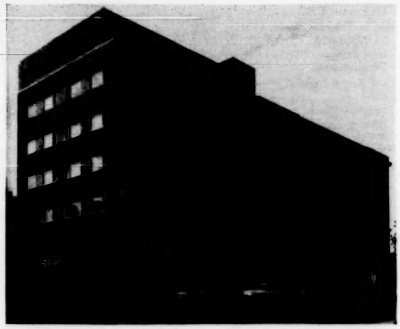
The proposed five-story Research Center Building will be a wing added to the recently built James A. Gray Memorial Building, which doubled the school's space when it was opened in 1958.

NORTH DAKOTA

Dedicate Hospital Addition in Minot.—Dedication ceremonies for the six-story, $2,500,000 addition to Trinity Hospital, Minot, were held Sept. 27, with Dr. Russell A. Nelson, Baltimore, president of the American Hospital Association and director of the Johns Hopkins Hospital, as the principal guest speaker. The institution now has a bed capacity of 250, reportedly making it the largest voluntary hospital in North Dakota. On the first floor of the addition and the remodeled original building are housed radiology, pathology, and bacteriology laboratories, a pharmacy, an emergency unit adjacent



The new six-story addition to Trinity Hospital, Minot.

to the ambulance entrance, a central supply depot, and the surgical suite. The latter provides eight major operating rooms, including two designed and equipped for urological and orthopedic surgery. The postoperative recovery rooms provide care for eight patients at a time. On the second floor are the rehabilitation wing, with 43 beds, and the division of physical medicine, including the departments of physical therapy, hydrotherapy and electrotherapy. Funds for the addition and remodeling were provided by private donors and the Hill–Burton Act in the amount of $325,000.

PENNSYLVANIA

Annual Lecture.—The Phi Delta Epsilon Fraternity, Nu Chapter, plans to hold the 14th annual R. R. Huggins Memorial Lecture on Nov. 5 at Nu Chapter, Pittsburgh. The speaker will be Dr. William Dameshek, Blood Research Laboratory, New England Center Hospital, Boston. The subject will be "Polycythemia Vera and Related States."

Tuberculosis Director Retires.—Dr. Morrison Clay Stayer, Harrisburg, director of the State Health Department's tuberculosis control program for 13 years announced his retirement, effective Sept. 4. Dr. Stayer was appointed to the State Health Department in August, 1946, following his retirement from a 38-year career in the United States Army Medical Corps. Dr. Harold E. Coder, Harrisburg, succeeds Dr. Stayer as director of the State Division of Tuberculosis Control. He has been chief of the tuberculosis hospitals under the administration of the State Department of Health.

Philadelphia

Annual Conference for Ex-Residents.—The 12th annual clinical conference of the staff and Society of Ex-Residents of Willis Eye Hospital will be held on Feb. 18-20, 1960. Clinic and hospital rounds will be held the morning of Feb. 18 and special surgical clinics in the afternoon. On the evening of Feb. 18, there will be a scientific meeting of the ophthalmological section of the Philadelphia College of Physicians which will be preceded by dinner. Dr. Levon K. Garron, of Oakland, Calif., will be the guest speaker. On Feb. 19 the scientific program will include individual presentations and color television surgery. The Arthur J. Bedell Lecture will be delivered on Feb. 20 by Dr. Peter C. Kronfeld, of Chicago. The conference will be concluded by a dinner meeting of the society that evening.

GENERAL

Clinical and Climatological Meeting.—The 72nd meeting of the American Clinical and Climatological Association will be held Nov. 2-4 at the Homestead, Hot Springs, Va. Dr. George W. Thorn, Boston, will present the presidential address preceding the presentation of formal papers. The Gordon Wilson Lecture, "Studies on the Effect of Vitamin B_1 Deficiency on the Human Nervous System," will be given by Dr. Raymond D. Adams, Boston. Seventeen other papers are scheduled. A business meeting is planned for the morning of Nov. 4. For information, write Dr. Fred T. Billings Jr., 420 Medical Arts Building, Nashville 12, Tenn.

Meeting on Fractures in New Orleans.—The American Fracture Association will hold its 20th annual meeting Nov. 1-4 at the Roosevelt Hotel, New Orleans, with the program acceptable for category II credit by the American and Louisiana academies of general practice. Industrial courses Nov. 1 will be acceptable for category I. Dr. Duncan C. McKeever, Houston, Texas, president of the association, will open the meeting and moderate the first session. Fifteen round-table discussions are planned for the afternoon of Nov. 1. A symposium, "External Pinning," will be moderated by Dr. Alvin H. Diehr, St. Louis. A second symposium, the H. D. Junkin,

M.D., Memorial, on the subject, "Ostamer," will be moderated by Dr. Earl D. McBride, Oklahoma City, Okla. For information, write Dr. Hermann W. Wellmerling, 610 Griesheim Bldg., Bloomington, Ill., Executive Secretary.

Meeting of Inhalation Therapists.—The fifth annual meeting and lecture series of the American Association of Inhalation Therapists will be held Nov. 16-20 at the Benjamin Franklin Hotel, Philadelphia. The five-day meeting will include medical lectures, round-table discussions, a field trip to a hospital, and the annual business meeting and election of new officers. The A.A.I.T. is a paramedical association whose objective is "to advance the art and science of inhalation therapy in the treatment of pulmonary and heart disorders." It is sponsored by the American College of Chest Physicians and the American Society of Anesthesiologists. It has 18 chapters and about 800 members in the United States and Canada. A featured speaker will be Dr. Kenneth L. Stratton, medical director, American Airlines, Inc., Flushing, N. Y., who will discuss "Oxygen and the Space Age."

Meeting on Gastroenterology Research.—The ninth semi-annual meeting of the Gastroenterology Research Group will be held Nov. 6 at the Drake Hotel, Chicago. A symposium, "The Biology of the Colonic Mucosa," will be moderated by Dr. Thomas P. Almy, New York City. Four papers are scheduled for presentation as follows:

Cellular Proliferation and Renewal in the Colonic Epithelium, Bernard Messier, Ph.D., Montreal, Canada.

Healing of the Colonic Mucosa, Dr. George D. Lumb, Memphis, Tenn.

The Role of the Normal Intestinal Flora in Antibody Production, Dr. Helmut A. Gordon, Niles, Mich.

Hypersensitivity Reactions in the Colonic Mucosa, Dr. Joseph B. Kirsner, Chicago.

A general session will follow the papers. The gastroenterology research dinner will be held at 5:30 p. m. The 10th semiannual meeting of the group will be held at the Roosevelt Hotel, New Orleans, March 31, 1960.

Southern Medical Meeting in Atlanta.—The Southern Medical Association will meet Nov. 16-19 at the Atlanta Municipal Auditorium, Atlanta, Ga., under the presidency of Dr. Milford O. Rouse, Dallas, Texas. Four major general sessions and 20 section meetings are scheduled. Two of the general sessions, one in medicine and one in surgery, will be presented Nov. 16. The others, in geriatrics and in nuclear medicine, will be presented Nov. 19. The Southern Flying Physicians and other socieites will meet conjointly. Scientific color television programs will be held Nov. 16-18. The annual dinner dance will be held Nov. 18, 7 p.m. Scientific and technical exhibits are planned, and a ladies' program is arranged. The annual golf tournament will be held Nov. 16-17. A postconvention tour to Nassau is planned. For information, write the Southern Medical Association, 2601 Highland Ave., Birmingham 5, Ala.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	Oct. 3, 1959 Paralytic Type	Oct. 3, 1959 Total Cases	Oct. 4, 1958 Total
New England States			
Maine	4	4	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	8	9	3
Rhode Island	..	..	..
Connecticut	2	2	..
Middle Atlantic States			
New York	22	29	13
New Jersey	6	8	18
Pennsylvania	15	18	5
East North Central States			
Ohio	9	12	35
Indiana	5	13	7
Illinois	6	17	17
Michigan	13	30	98
Wisconsin	5	5	6
West North Central States			
Minnesota	15	20	2
Iowa	6	9	6
Missouri	11	16	8
North Dakota	..	1	3
South Dakota	..	..	..
Nebraska	3	6	1
Kansas	3	5	..
South Atlantic States			
Delaware	..	..	..
Maryland	3	3	1
District of Columbia	..	..	..
Virginia	6	8	3
West Virginia	6	6	11
North Carolina	12	19	9
South Carolina	2	5	1
Georgia	8	12	..
Florida	1	2	3
East South Central States			
Kentucky	19	21	4
Tennessee	29	34	5
Alabama	3	3	1
Mississippi	..	..	11
West South Central States			
Arkansas	7	10	1
Louisiana	4	7	1
Oklahoma	5	6	2
Texas	2	9	18
Mountain States			
Montana	..	..	3
Idaho	..	..	..
Wyoming	..	..	..
Colorado	1	1	2
New Mexico	1	1	..
Arizona	..	1	1
Utah	..	..	2
Nevada	..	1	..
Pacific States			
Washington	13	13	..
Oregon	8	10	..
California	16	17	12
Alaska	..	..	..
Hawaii	..	..	2
Territories and Possessions			
Puerto Rico	..	1	..
Total	279	394	315

Obstetricians and Gynecologists Meet in Hawaii.—The sixth annual meeting of District VIII, The American College of Obstetricians and Gynecologists, will be held at the Royal Hawaiian Hotel, Honolulu, Hawaii, Nov. 15-22. District VIII comprises Alaska, Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming, Alberta, British Columbia, and Hawaii. The scientific program will consist of 15 formal papers, 20 round tables, and 45 breakfast conferences. Two days will be devoted to visits to hospitals and clinics in Honolulu. Dr. George E. Judd, Los Angeles, District VIII chairman, will open the meeting. Among the participants in the scientific program will be Drs. John I. Brewer, Chicago, president of ACOG; Robert G. Craig, San Francisco, immediate past-president; and Craig W. Muckle, Philadelphia, secretary. The entertainment program includes a luau and dinner dance. For information, write Dr. George E. Judd, 2010 Wilshire Blvd., Los Angeles 57, or Mr. Donald F. Richardson, executive secretary, ACOG, 79 W. Monroe St., Chicago 3.

Medical Imposter.—One Clarence H. Cypher has represented to the Board of Medical Examiners of the State of Arizona and to others that he is a doctor of medicine. Cypher is described as having obtained money from several persons on the representation that he is a physician. A thorough check of the biographic records at A. M. A. headquarters, however, does not reveal that a man by that name has ever been a medical student or a graduate in medicine. Cypher is described as one acquainted with medical terminology and customs, possibly acquired while employed as a technician or in some similar paramedical capacity. He is between 35 and 38 years of age, about 5 ft. 7 in. in height, weighing 135-140 lbs., thin, having a long, sharp nose, blue eyes, and gray hair. Cypher has represented himself as a physician in Douglas and Phoenix, Ariz., and Germantown, Ky. He has claimed graduation from the University of Michigan Medical School and/or the Chicago Medical School. Anyone having knowledge of his whereabouts should contact the Department of Investigation at A. M. A. headquarters or the Executive Secretary of the Board of Medical Examiners of the State of Arizona at Phoenix.

Annual Symposium on Antibiotics.—The seventh annual Symposium on Antibiotics, sponsored by the journals *Antibiotics & Chemotherapy* and *Antibiotic Medicine & Clinical Therapy*, will be held Nov. 4-6 at the Mayflower Hotel, Washington, D. C. The symposium will open with a general session dedicated to "The Challenge of New Drugs in Our Society." Dr. Felix Marti-Ibanez, New York City, will inaugurate this session with a talk, "The Great Historical Challenges in Medicine," and Drs. Austin E. Smith, Washington, D. C., Maxwell Finland, Boston, William H. Kessenich, Washington, D. C., and John G. Quarry, Burlington, Ont., will discuss the following: "The Challenge of New Drugs to the Pharmaceutical Industry," "The Challenge of New Drugs to the Clinical Investigator," "The Challenge of New Drugs to the U. S. Food and Drug Administration," and, finally, "The Challenge of New Drugs to the Practicing Physician." Two panel discussions are planned: The Present Status and Problems Involved in Human Sensitization to Antibiotics, and Chemotherapy of Acute and Chronic Pediatric and Geriatric Infections. For information, write Henry Welch, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C.

Postgraduate Medical Meeting.—The 44th international medical assembly of the Interstate Postgraduate Medical Association of North America will be held Nov. 2-5 at the Palmer House, Chicago. The program includes the following panel discussions and moderators:

Massive Intestinal Hemorrhage, Dr. Alton Ochsner, New Orleans.
Renal Failure, Dr. Robert M. Kark, Chicago.
Emergencies in the First Day of Life, Dr. Willis J. Potts, Chicago.
Non-Toxic Goiter, Dr. George Crile Jr., Cleveland.
The Place of Pitocin in Obstetrical Practice, Dr. Herbert E. Schmitz, Chicago.
Resistant Staphylococcus Infections, Dr. Edgar J. Poth, Galveston.
Medical Aspects of Modern Submarine Warfare, Capt. Gerald J. Duffner, MC, USN, Washington, D. C.
Newer Developments in Diuretics, Dr. John H. Moyer, Philadelphia.
Treatment of Multiple Injuries Associated with Auto Accidents, Dr. George J. Curry, Flint, Mich.
Evaluation of the Acute Abdomen, Dr. Robert M. Zollinger, Columbus, Ohio.

A surgical symposium is planned for the afternoon of Nov. 4, at which Dr. Samuel F. Marshall, Boston, will present "Carcinoma of the Stomach" as the Arthur G. Sullivan Memorial Lecture. Breakfast conferences and teaching demonstrations are scheduled. At the annual dinner Nov. 4, Kenneth McFarland, Ph.D., Topeka, Kan., will present, "3-Dimensional Confidence." Scientific and technical exhibits are arranged, and a ladies' program is planned. For information, write the Interstate Postgraduate Medical Association, P. O. Box 1109, Madison 1, Wis.

CORRECTIONS

Dr. William Herbert Burwig Not Dead.—The report of death of Dr. William Herbert Burwig, of Buffalo, N. Y., which appeared in THE JOURNAL, Oct. 3, page 573, was erroneous. William Burwig of Buffalo, reported as dead by the New York State Department of Health, was a naturopath.

Foreign Speakers at Gastroenterology Meeting.—In the Sept. 19 issue of THE JOURNAL, page 317, in an item announcing the 24th convention of the American College of Gastroenterology the following should have been listed as foreign speakers: Dr. Xavier de la Riva, Mexico; Dr. Sylvio Markees, Basel, Switzerland; Dr. Octavio Montanez, Mexico; Dr. Jordan T. Propatoridis, Athens, Greece; and Dr. Francisco Puente Pereda, Mexico.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. March 16, 1960 and Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 19-20. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 21-23, 1960. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ALASKA:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

ARKANSAS:* *Examination and Reciprocity.* Little Rock, Nov. 5-6. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Oral.* San Francisco, November 14. *Oral and Clinical.* San Francisco, Nov. 15. Sec., Dr. Lous E. Jones, Room 536, 1020 N Street, Sacramento.

COLORADO:* *Examination.* Denver, Dec. 8-9. *Reciprocity.* Denver, Oct. 14. Exec. Sec., Miss Mary M. McConnell, 715 Republic Bldg., 1612 Tremont Place, Denver 2.

CONNECTICUT:* *Examination.* Hartford, Nov. 10-12. Sec. to the Board, Dr. Stanley B. Weld, 160 St. Ronan St., New Haven.

DELAWARE: *Examination.* Dover, Jan. 12-14. *Endorsement.* Dover, Jan. 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

DISTRICT OF COLUMBIA:* *Examination.* Washington, Dec. 14-15. *Reciprocity.* Washington, Sept. 14. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., Washington 6.

FLORIDA:* *Examination.* Miami Beach, Nov. 22-24. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

GUAM: *Subject to Call.* Act. Sec., Dr. F. L. Conklin, Agana.

HAWAII: *Examination.* Honolulu, Jan. 11-12. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: *Examination* and *Reciprocity.* Boise, Jan. 11, 12, 13. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

INDIANA: *Examination.* Indianapolis, June 1960. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

KANSAS:* *Examination and Reciprocity.* Kansas City, Jan. 15-16. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Frankfort, Dec. 14-15. Asst. Sec., Mrs. Ray Wunderlich, 620 South Third St., Louisville 2.

LOUISIANA: *Examination and Reciprocity.* New Orleans, Dec. 3-5. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

MAINE: *Examination* and *Reciprocity.* Portland, Nov. 10. Sec., Dr. Stephen A. Cobb, Stanford.

MARYLAND: *Examination.* Baltimore, Dec. 8-11, Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination.* Boston, Jan. 12-15. Sec., Dr. David W. Wallwork, Room 37, State House, Boston.

MINNESOTA:* *Examination.* Jackson, June 1960. *Reciprocity.* Jackson, Dec. 7, Sec., Dr. A. L. Gray, Old Capitol, Jackson.

NEBRASKA:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

NEW JERSEY: *Examination.* Jan. 19-22. *Reciprocity.* Monthly, Sec., Dr. Royal A. Schaaf, 28 West State St., Trenton.

NEW MEXICO:* *Examination and Reciprocity.* Santa Fe, Nov. 16-17. Sec., Dr. C. Derbyshire, 227 East Palace Ave., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Dec. 8-11. Sec., Dr. Stiles D. Ezell, 23 South Pearl St., Albany.

NORTH DAKOTA: *Examination.* Grand Forks, Jan. 6-8. *Reciprocity.* Grand Forks, Jan. 9. Sec., Dr. C. J. Glaspel, Box 228, Grafton.

OHIO: *Examination.* Columbus, Dec. 15-17. *Endorsement.* Columbus, Oct. 5. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus 15.

PENNSYLVANIA: *Examination.* Philadelphia, January. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

SOUTH CAROLINA: *Examination and Endorsement.* Columbia, Dec. 8. Sec., Dr. H. E. Jervey, Jr., 1329 Blanding St., Columbia.

TEXAS:* *Examination.* Fort Worth, Dec. 3-5. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 6-8. *Reciprocity.* Salt Lake City, Nov. 17. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

VIRGINIA: *Reciprocity.* Dec. 1, *Examinations* Dec. 2-4 inclusive, Richmond. Address: Board of Medical Examiners, 631 First St. S. W., Roanoke.

VIRGIN ISLANDS: *Examination.* Charlotte Amalie, Nov. 12-13. Sec., Dr. Benjamin Nath, Charlotte Amalie, St. Thomas.

WASHINGTON:* *Examination.* Seattle, Jan. 11-13. Administrator, Professional Division, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination.* Charleston, January. Sec., Dr. Newman H. Dyer, State Office Bldg., No. 3, Charleston 5.

WISCONSIN:* *Examination.* Madison, Jan. 14-16. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Building, 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, Feb. 1. Sec., Dr. James W. Sampson, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination and Reciprocity.* Juneau, November. Sec., Dr. R. Harrison Leer, Alaska Office Bldg., Juneau.

DISTRICT OF COLUMBIA: *Examination.* Washington, Nov. 23-24. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., Washington 6.

FLORIDA: *Examination.* Gainesville, Nov. 7. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

KANSAS: *Examination.* Pittsburg, Nov. 6-7. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

RHODE ISLAND: *Examination.* Providence, Nov. 18. *Reciprocity.* Providence, Nov. 4. Administrator, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA: *Examination.* Vermillion, Dec. 4-5. Dr. Gregg M. Evans, 310 East 15th St., Yankton.

WASHINGTON: *Examination.* Seattle, Jan. 6-7. Sec., Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WISCONSIN: *Examination.* Milwaukee, Dec. 5, Madison, Apr. 9, Sec., Mr. Wm. H. Barber, 621 Ranson St., Ripon.

*Basic Science Certificate required.

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DEATHS

Abraham, Ernest Guenter Ⓜ New York City; Albertus–Universität Medizinische Fakultät, Konigsberg, Prussia, Germany, 1926; fellow of the International College of Surgeons of which he was a vice-president and associate secretary; associated with the Mount Sinai Hospital; died Aug. 17, aged 57.

Adams, Leslie Pleasant, New York City; Emory University School of Medicine, Atlanta, 1931; interned at Nassau Hospital in Mineola, N. Y.; served a residency at the Neurological Institute of New York in New York City, and the Brooklyn State Hospital; certified by the National Board of Medical Examiners; specialist certified by the American Board of Psychiatry and Neurology; associated with the Neurological Institute, Presbyterian Hospital, and Vanderbilt Clinic; died Aug. 4, aged 57.

Adams, Robert Albert, Whitestone, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1904; veteran of World War I; on the staff of the Flushing (N. Y.) Hospital; died Aug. 3, aged 79.

Alpert, Theodore Nathaniel, Ventura, Calif.; University of Buffalo School of Medicine, 1912; died Aug. 5, aged 72.

Ames, Frederick Daniel Ⓜ Houston, Texas; Harvard Medical School, Boston, 1933; veteran of World War II and won both the Purple Heart and Bronze Star for service in the Southwest Pacific; past-president of the Harris County Pediatrics Society; died in the Veterans Administration Hospital Aug. 12, aged 52.

Asborno, John Nicholas Ⓜ Denver; Creighton University School of Medicine, Omaha, 1956; interned at St. Anthony Hospital; for two years served in the U. S. Air Force; died Aug. 14, aged 28.

Barr, Herman Paul Ⓜ Chicago; Northwestern University Medical School, Chicago, 1921; associated with the South Shore and Little Company of Mary hospitals; died Aug. 22, aged 65.

Bivins, Luther Lee, Copperas Cove, Texas; University of Louisville (Ky.) Medical Department, 1900; at one time city health officer; died in the King's Daughters Hospital in Temple July 25, aged 79.

Bolt, Richard Arthur, Berkeley, Calif.; born in St. Louis March 12, 1880; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1906; served on the faculty of Western Reserve University School of Medicine in Cleveland and the University of California in Berkeley; at one time lecturer at Johns Hopkins University School of Hygiene and Public Health in Baltimore; formerly a director of the Cleveland Child Health Association and chief of the bureau of child hygiene for the department of health of Cleveland; in 1917-1918 director of the United States indemnity program in Peking, China; received two decorations from the Chinese Red Cross for his work during the Chinese Revolution; in 1918-1919 director of the child welfare division of the tuberculosis commission of the American Red Cross in Italy; formerly consultant on maternal and infant hygiene for the U. S. Children's Bureau; served as a member of the White Conference on Child Health and Protection; formerly editor of the child health section of the *Journal of the American Public Health Association;* died in Alta Bates Hospital Aug. 3, aged 79.

Boughton, Geoffrey Allyn Ⓜ Captain, U. S. Army, retired, Larchmont, N. Y.; Boston University School of Medicine, 1954; certified by the National Board of Medical Examiners; interned at the Massachusetts Memorial Hospitals in Boston, where he served a residency; entered the U. S. Army in July, 1957; died in the Walter Reed Army Hospital in Washington, D. C., June 30, aged 30.

Bowen, Robert E. Ⓜ San Antonio, Texas; University of Texas School of Medicine, Galveston, 1903; a division surgeon for Southern Pacific Lines; died in Gonzales Aug. 13, aged 80.

Chamberlain, Herbert Denison Ⓜ McArthur, Ohio; Ohio State University College of Medicine, Columbus, 1933; member of the American Academy of General Practice; veteran of World War I; president of the county board of health; formerly county health officer; died in the Mount Carmel Hospital in Columbus Aug. 10, aged 60.

Cogan, Julius, Reseda, Calif.; Georgetown University School of Medicine, Washington, D. C., 1927; associated with the Olive View (Calif.) Sanatorium; died in the Kaiser Foundation Hospital in Los Angeles Aug. 7, aged 62.

Cole, Norman Brown Ⓜ Baltimore; Harvard Medical School, Boston, 1914; member of the Association of Life Insurance Medical Directors of America; veteran of World War I; medical director and secretary of the Baltimore Life Insurance Company and a member of its board of directors;

Ⓜ Indicates Member of the American Medical Association.

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for many years a member of the school board; interested in youth problems, spent much of his leisure time as a scoutmaster, troop committeeman, and was president of the Baltimore Area Council of the scouts; associated with Johns Hopkins Hospital; died in Nantucket, Mass., Aug. 18, aged 73.

Custer, Byron Homer, North Little Rock, Ark.; Kansas City (Mo.) College of Medicine and Surgery, 1926; died Aug. 3, aged 56.

Dean, George Brookhouse, Medford, Ore.; Miami Medical College, Cincinnati, 1898; died in the Rogue Valley Memorial Hospital Aug. 3, aged 86.

De Sautelle, William Thomas Ⓜ Knoxville, Tenn.; Johns Hopkins University School of Medicine, Baltimore, 1911; fellow of the American College of Physicians; served on the staffs of Knoxville General, Fort Sanders Presbyterian, and St. Mary's Memorial hospitals; died Aug. 9, aged 74.

Dorne, Philip Harry Ⓜ Chicago; Northwestern University Medical School, Chicago, 1914; member of the American Academy of Dermatology and Syphilology; staff member at Alexian Brothers Hospital; veteran of World War I; died Aug. 20, aged 69.

Duggan, Henrietta Hagan Ⓜ San Francisco, Calif.; University of California School of Medicine, San Francisco, 1903; served on the staffs of the University of California, Children's, and St. Mary's hospitals; died Aug. 7, aged 78.

Dunbar, Helen Flanders Ⓜ New York City; born in Chicago May 14, 1902; Yale University School of Medicine, New Haven, Conn., 1930; specialist certified by the American Board of Psychiatry and Neurology; certified by the National Board of Medical Examiners; fellow of the New York Academy of Medicine, American Psychiatric Association, of which she was secretary treasurer, 1939-1940, American Geriatrics Society, International Association of Gerontology, and the New York Academy of Science; member of the American Association for the Advancement of Science, New York Society of Clinical Psychiatry, American Psychoanalytic Association, treasurer from 1942 to 1945, American Psychopathological Association, serving as vice-president from 1942 to 1945, Association for Research in Nervous and Mental Diseases, International Psychoanalytic Association, National Committee on Alcoholism, National Safety Council, New York State Academy of General Practice, World Medical Association, American Orthopsychiatric Association, American Psychosomatic Society, American Committee for World Federation for Mental Health, and Greenwich Medical Society; served on the faculty of Columbia University College of Physicians and Surgeons, and from 1941 to 1949 instructor at New York Psychoanalytic Institute; at various times associated with the Bellevue, Presbyterian, and Greenwich (Conn.) hospitals, and the Vanderbilt Clinic; editor in chief emeritus of *Psychosomatic Medicine*, of which she was editor in chief from 1938 to 1947; collaborating editor from 1938 to 1940 and editor, 1939-1940, *Psychoanalytic Quarterly;* author of "Symbolism in Medieval Thought," "Emotions and Bodily Changes," "Psychosomatic Diagnosis," "Your Child's Mind and Body," "Mind and Body," and "Psychiatry in the Medical Specialties"; died Aug. 21, aged 57.

Faucett, Robert Lynn Ⓜ Rochester, Minn.; born in Independence, Mo., April 6, 1916; University of Kansas School of Medicine, Kansas City, Mo., 1944; interned and was resident in pediatrics at the University of Kansas Hospitals in Kansas City, Kan., from 1944 to 1946; in December, 1946, commissioned a senior assistant surgeon in the U. S. Public Health Service, assigned to the USPHS Hospital in Lexington, Ky.; in July, 1948, was assigned by the USPHS to the department of psychiatry at the University of Minnesota for graduate study in pediatric psychiatry; came to Rochester a year later as a special worker with the former Rochester Child Health Institute; from January to June, 1950, a fellow in neurology and psychiatry in the Mayo Foundation; in March of that year became a part-time psychiatric consultant at the Counselling Clinic of the Rochester–Olmsted County Public Health Center, and on July 1 was appointed director of the Counselling Clinic for a term of six months; left Rochester in January, 1951, to become director of the Prince Georges County Health Clinic at the University of Maryland in College Park, Md.; also continued psychoanalysis studies at the Washington Psychoanalytic Institute in graduate training; returned to Rochester on July 1, 1953, as a consultant in psychiatry in the Mayo Clinic; appointed instructor in psychiatry in the Mayo Foundation, Graduate School, University of Minnesota, in 1955, and was advanced to the grade of assistant professor in 1959; in 1957 was a member of the faculty at the first workshop on psychological problems of pastoral care at St. John's University in Collegeville, Minn.; specialist certified by the American Board of Psychiatry and Neurology; member of the Minnesota Psychiatric Society, American Psychosomatic Society, the Society of the Sigma Xi and the Alumni Association of the Mayo Foundation; fellow of the American Psychiatric Association; died Aug. 5, aged 43.

Glodt, Milton, Boston; Universität Basel Medizinische Fakultät, Switzerland, 1936; died in Nantucket, Mass., Aug. 14, aged 56.

Goodman, Thomas L. Ⓜ Fort Worth, Texas; Fort Worth School of Medicine, Medical Department of Texas Christian University, 1913; past-president of the Tarrant County Medical Society; served on the staffs of City and County Hospital and St. Joseph's Hospital; died Aug. 4, aged 77.

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Graham, James Jahue, Marion, S. C.; Meharry Medical College, Nashville, Tenn., 1928; died Aug. 17, aged 72.

Gregg, Arthur William Ⓜ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; member of the senior surgical staff, Walther Memorial Hospital; died Aug. 26, aged 76.

Haining, Lois Nicolini, San Francisco; Stanford University School of Medicine, San Francisco, 1956; interned at the Los Angeles County Hospital; served a residency at the Veterans Administration Hospital in Iowa City, Iowa; died in Pacifica July 28, aged 28.

Hart, George H., Davis, Calif.; George Washington University School of Medicine, Washington, D. C., 1908; member of the Endocrine Society; dean emeritus, University of California School of Veterinary Medicine; died in Woodland, Aug. 2, aged 75.

Harvey, Fredric Everett Ⓜ Minneapolis, Kan.; Kansas City (Mo.) Medical College, 1905; veteran of World War I; during World War II Selective Service examiner; served as health officer of Ottawa County; formerly on the staffs of St. John's and Asbury hospitals in Salina; died in the Concordia (Kan.) Hospital Aug. 6, aged 77.

Hass, Julius Ⓜ New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1910; member of the American Academy of Orthopaedic Surgeons; fellow of the International College of Surgeons; associated with the Hospital for Special Surgery, Montefiore Hospital, Madison Avenue Hospital, and the Manhattan General Hospital; died Aug. 17, aged 76.

Hatton, Edward Howard, Evanston, Ill.; Rush Medical College, Chicago, 1912; for many years professor of pathology at Northwestern University Dental School; served on the faculty of his alma mater from 1917 to 1919; coroner's physician for Cook County from 1916 to 1923; past-president and secretary-treasurer of the International Association for Dental Research; died in the Evanston Hospital Aug. 15, aged 83.

Haury, Paul Gerhardt Ⓜ Lewiston, Idaho; Northwestern University Medical School, Chicago, 1929; fellow of the American College of Surgeons; past-president of the North Idaho Medical Society; veteran of World War II; formerly member of the city council; on the staff of St. Joseph's Hospital; died Aug. 9, aged 59.

Hazzard, Lawrence Rosseau, Portsmouth, N. H.; University of Kansas School of Medicine, Kansas City, Kan., 1918; fellow of the American College of Surgeons; past-president of the New Hampshire Surgical Club; veteran of World War I; associated with the Portsmouth Hospital, where he died Aug. 10, aged 70.

Healy, Merritt Wood Ⓜ Norfolk, Va.; University College of Medicine, Richmond, 1906; served overseas during World War I; for many years surgeon for the Norfolk Shipbuilding and Drydock Corporation; died Aug. 14, aged 76.

Hill, Irvin Bartle Ⓜ Salem, Ore.; University of Oregon Medical School, Portland, 1939; interned at the Good Samaritan Hospital in Portland; served a residency at the Oregon State Hospital; member of the American Psychiatric Association; served as vice-president of the American Association of Mental Deficiency; on the faculty of his alma mater; administrator, Oregon Fairview Home; died Aug. 17, aged 44.

Hinton, William Augustus Ⓜ Boston; born in Chicago Dec. 15, 1883; Harvard Medical School, Boston, 1912; the first Negro ever awarded a professorship at Harvard, where in 1949 he was appointed clinical professor of bacteriology and immunology, and held teaching positions for many years; from 1919 to 1953 lecturer at Simmons College; chief of clinical laboratories of the Boston Dispensary from 1916 to 1952; served as chief of the laboratories of the Boston Floating Hospital; a director of the Committee on Research and Syphilis, Inc.; for many years a special consultant to the U. S. Public Health Service and consultant to the Massachusetts School for Crippled Children; on Dec. 31, 1953, retired after 38½ years of service as director of the Wassermann Laboratory of the Massachusetts Department of Public Health, and Governor Christian A. Herter commended him "both as a noted scientist and faithful servant of the Commonwealth"; devised the Hinton Test for the detection of syphilis, used by the U. S. Armed Forces, hospitals, clinics, and public health laboratories throughout the world; with the assistance of Dr. John A. V. Davies, of Children's Hospital, also developed the Davies–Hinton test, a test on spinal fluids for the detection of syphilis in the nervous system; served as a member of the American Society of Clinical Pathologists, the Society of American Bacteriologists, the American Association for the Advancement of Science, and the American Public Health Association; author of "Syphilis and Its Treatment" published in 1936; died Aug. 8, aged 75.

Hitchcock, John Phinizy Ⓜ Augusta, Ga.; Medical College of Georgia, Augusta, 1936; interned at the University Hospital, where he served a residency; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; veteran of World War II; on the staffs of St. Joseph's Hospital and the University Hospital, where he died Aug. 7, aged 48.

Horwitz, Ellis Berry Ⓜ Philadelphia; Medico-Chirurgical College of Philadelphia, 1915; served during World War II; died in the Temple University Hospital Aug. 17, aged 67.

Houghton, Montafix Wilson Ⓜ Providence, R. I.; George Washington University School of Medicine, Washington, D. C., 1904; veteran of World War I; retired acting assistant surgeon in the U. S. Public Health Service; associated with the Roger Williams General Hospital; died Aug. 9, aged 79.

Houston, David H. Ⓜ Seattle; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1903; past-president of the Washington State Obstetrical Association, King County Medical Society, and Washington State Golfing Association; a past-president of the American Medical Golfing Association, of which he was permanent chairman; a trustee, formerly chief of obstetrics, and an honorary staff member, Virginia Mason Hospital; served as chief of obstetrics at King County Hospital and on the staff of the Doctors Hospital; died Aug. 4, aged 78.

Hutnick, Stephen Emanuel, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1920; died July 2, aged 64.

Jackson, Arthur Husted, Watkins Glen, N. Y.; Syracuse University College of Medicine, 1904; for many years county coroner; served as a member and president of the board of education of Odessa and Watkins Glen; associated with the Willard (N. Y.) State Hospital and the Schuyler Hospital in Montour Falls, where he died Aug. 14, aged 80.

James, Francis Marshall Jr. Ⓜ Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1930; associated with the Memorial Hospital, where he died Aug. 7, aged 55.

Janss, Edwin, Los Angeles; Northwestern University Medical School, Chicago, 1903; veteran of World War I; died in St. John's Hospital, Santa Monica, Aug. 19, aged 77.

Johnson, Cecil Emerson Ⓜ Rensselaer, Ind.; Northwestern University Medical School, Chicago, 1910; veteran of World War I; served as county health officer; died in St. Elizabeth Hospital, Lafayette Aug. 2, aged 70.

Jones, Ralph Northrup, Whitefield, N. H.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1931; veteran of World War I; associated with the Morrison Hospital, where he died Aug. 6, aged 61.

Kaufman, Charles, New London, Conn.; Jefferson Medical College of Philadelphia, 1919; fellow of the American College of Surgeons; served on the staff of the Lawrence and Memorial Hospitals; died Aug. 8, aged 64.

Keppler, Charles Jr., Mount Shasta, Calif.; University of Virginia Department of Medicine, Charlottesville, 1930; also a graduate in pharmacy; died Aug. 14, aged 55.

Kimble, James Norman Ⓜ Takoma Park, Md.; College of Medical Evangelists, Loma Linda and Los Angeles, 1933; specialist certified by the American Board of Radiology, Inc.; member of the American College of Radiology; past-president of the Montgomery County Medical Society; interned, and for many years director of radiology at the Washington Sanitarium and Hospital, where he died Aug. 13, aged 73.

Kirkpatrick, Milton Barnes Ⓜ Montgomery, Ala.; Medical Department of Tulane University of Louisiana, New Orleans, 1896; for many years coroner of Montgomery County; associated with the Fitts Hill Hospital and St. Margaret's Hospital, where he died Aug. 8, aged 88.

Kirkwood, Elmer Earle Ⓜ Youngstown, Ohio; St. Louis University School of Medicine, 1919; member of the American College of Chest Physicians and past-president of the Ohio Chapter; member of the American Academy of General Practice; for many years associated with the Mahoning Tuberculosis Sanatorium, of which he was medical director; served on the staff of the Cleveland Municipal Tuberculosis Sanatorium in Warrenville, Ohio; died in the North Side unit of the Youngstown Hospital Aug. 14, age 65.

Kirwin, Thomas Joseph Ⓜ New York City; born in Scranton, Pa., Aug. 31, 1889; Tulane University School of Medicine, New Orleans, 1916; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons and the International College of Surgeons; served on the faculty as professor of urology at New York Medical College, Flower and Fifth Avenue Hospitals; veteran of World War I; associated with the Flower and Fifth Avenue, Metropolitan, Bird S. Coler, and New York hospitals, New York City, Coney Island Hospital, Brooklyn, Benedictine Hospital, Kingston, N. Y., Monmouth Memorial Hospital in Long Branch, Passaic (N. J.) Hospital, and South Nassau Communities Hospital in Rockville Centre; joint author of "Textbook of Urology," "Urology for Nurses," and two volumes of "Clinical Urology"; died in the New York Hospital Aug. 18, aged 69.

Kraus, Karl Joseph, Las Vegas, Nev.; University of Cincinnati College of Medicine, 1934; veteran of World War II; died Aug. 5, aged 51.

Laughlin, Judson, Clarion, Iowa; Central Medical College of St. Joseph, Mo., 1896; associated with the Clarion Memorial Hospital, where he died July 21, aged 91.

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Little, William Bracey, Plaquemine, La.; Meharry Medical College, Nashville, Tenn., 1912; died Aug. 6, aged 79.

McDevitt, Daniel Robert Ⓜ Indianapolis; Indiana University School of Medicine, Indianapolis, 1923; member of the American Academy of General Practice; associated with St. Vincent's, Methodist, and St. Francis hospitals; died Aug. 15, aged 62.

McKinstry, Herbert Sydney Ⓜ Kennett Square, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1917; member of the American Academy of General Practice; at one time president of the Chester County Medical Society; served overseas during World War I; associated with the West Chester (Pa.) Memorial Hospital; on the courtesy staff of Chester County Hospital in West Chester, and the Memorial Hospital, Wilmington, Del., where he died Aug. 7, aged 70.

McLaughlin, James Francis Ⓜ Adams, Mass.; Tufts College Medical School, Boston, 1919; veteran of World War I; for many years member of the board of health; formerly medical consultant for the Adams Welfare Department; past-president of the Adams Anti-Tuberculosis Association; associated with the Plunkett Memorial Hospital; died Aug. 11, aged 64.

McNaught, James Bernard Ⓜ Denver; born in Girard, Kan., July 11, 1894; Stanford University School of Medicine, San Francisco, 1931; served as head of the department of pathology at the University of Colorado School of Medicine, where he was professor of pathology; instructor in bacteriology at the University of Kansas, Lawrence, from 1919 to 1921; joined the faculty of his alma mater as an assistant in pathology, subsequently becoming instructor, assistant professor, and associate professor of pathology; in 1934-1935 exchange instructor of pathology at the University of Rochester (N. Y.) School of Medicine and Dentistry; from 1937 to 1945 director and pathologist at the Palo Alto (Calif.) Hospital; veteran of World War I; since 1948 consultant to Atomic Energy Commission, Division of Biology and Medicine; expert consultant to Surgeon General, U. S. Army, since 1946; consultant in pathology to Surgeon General of the U. S. Air Force since 1952; area consultant in pathology, St. Louis Medical Area, Veterans Administration since 1946; member of the scientific advisory board of consultants to Armed Forces Institute of Pathology; specialist certified by the American Board of Pathology, of which he was a trustee from 1944 to 1956, and president from 1953 to 1955; member of the American Association of Pathologists and Bacteriologists, of which he was councilor in 1949 and later president; founding fellow and past-governor of the College of American Pathologists; member and past-president of the American Society of Clinical Pathologists and in 1957 received its Certificate of Highest Merit; formerly councilor, vice-president, and president of the International Association of Medical Museums; past-president of the International Academy of Pathology; charter member of the American Physicians Art Association; member of the American Society for Experimental Pathology, American Association for the Advancement of Science, American Society of Tropical Medicine, American Society for Parasitology, Federation of American Societies for Experimental Biology, Society for Experimental Biology and Medicine, Alpha Kappa Kappa, Alpha Omega Alpha, Phi Delta Kappa, and Sigma Xi; died in the Veterans Administration Hospital, Albuquerque, N. M., Aug. 7, aged 65.

Mason, Charles Leonard Ⓜ Durango, Colo.; University of Colorado School of Medicine, Denver, 1932; interned at the Hillman Hospital in Birmingham, Ala., and the St. Joseph's Hospital in Denver; veteran of World War II; associated with the Mercy Hospital; died Aug. 5, aged 52.

May, Murray Morris, Brooklyn; Universität Bern Medizinische Fakultät, Switzerland, 1936; veteran of World War II; died June 6, aged 52.

Mattson, James Marshall Ⓜ Tacoma, Wash.; University of Pennsylvania School of Medicine, Philadelphia, 1939; interned at the Scott and White Hospital in Temple, Texas, where he served a residency; associated with the Tacoma General, St. Josephs, Medical Arts, and Doctors hospitals; died Aug. 1, aged 47.

Miears, Claude H. Ⓜ Austin, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1925; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; associated with the Brackenridge, Seton, and Holy Cross hospitals; on the honorary staff of St. David's Hospital; died Aug. 5, aged 64.

Miller, Isidore Ⓜ New York City; University and Bellevue Hospital Medical College, New York City, 1911; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World War I; associated with the New York Eye and Ear Infirmary and the Jewish Memorial Hospital; died Aug. 12, aged 75.

O'Connor, Dermot Fenton Ⓜ Syosset, N. Y.; University College, Dublin, Ireland, 1941; interned at the Doctors Hospital in New York City; associated with the Meadowbrook Hospital in Hempstead and the Community Hospital in Glen Cove, where he died July 21, aged 41.

Pennington, Alfred William Ⓜ Newark, Del.; Medical College of Virginia, Richmond, 1929; specialist certified by the American Board of Internal

Medicine; fellow of the American Academy of Occupational Medicine and the Industrial Medical Association; associated with the medical division of E. I. DuPont de Nemours Company; died Aug. 9, aged 56.

Phillips, Lawrence Curtis, Pensacola, Fla.; Hering Medical College, Chicago, 1903; died Aug. 5, aged 86.

Poirier, George Henri Ⓜ Boston; Tufts College Medical School, Boston, 1910; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological, Rhinological and Otological Society; veteran of World War I; associated with the Massachusetts Eye and Ear Infirmary; died Aug. 8, aged 73.

Potter, Caroline Colver, East Lansing, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1900; died Aug. 4, aged 81.

Roemer, Thomas Jacques Ⓜ Portland, Ore.; State University of Iowa College of Medicine, Iowa City, 1930; associated with the St. Vincent's Hospital, Providence Hospital, and the Good Samaritan Hospital, where he died Aug. 1, aged 58.

Saxon, Robert Lee Ⓜ Little Rock, Ark; University of Nashville (Tenn.) Medical Department, 1900; past-president of the Pulaski County Medical Society; formerly on the faculty of the University of Arkansas School of Medicine; served on the staffs of the St. Vincent Infirmary and the Arkansas Baptist Hospital; died in the Methodist Hospital in Houston, Texas, Aug. 9, aged 85.

Schofield, James Dobson Ⓜ Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1902; specialist certified by the American Board of Surgery and the American Board of Proctology; member of the American Proctologic Society; fellow of the American College of Surgeons; veteran of World War I; associated with Hahnemann Medical College and Hospital and the St. Luke's and Children's Medical Center; died at his home in Wynnewood, Pa., Aug. 9, aged 80.

Smith, Ellis Jacob Ⓜ Cincinnati; Eclectic Medical College, Cincinnati, 1925; served on the staff of St. Francis Hospital; died Aug. 8, aged 62.

Sutherland, Justus, Oshkosh, Wis.; Milwaukee Medical College, 1900; veteran of World War I; served on the staff of the Veterans Administration Hospital in Wood; died in the Mercy Hospital July 26, aged 83.

Symonds, Cleon Walter Ⓜ Redlands, Calif.; Harvard Medical School, Boston, 1910; veteran of World War I; fellow of the International College of Surgeons; died in the Loma Linda (Calif.) Sanitarium and Hospital July 26, aged 75.

Thomson, Robert Robertson, Berkeley, Calif.; University of California School of Medicine, San Francisco, 1928; served on the staff of the Ernest V. Cowell Memorial Hospital; died July 29, aged 71.

Ulfelder, Sidney, Mexico City, D. F., Mexico; Columbia University College of Physicians and Surgeons, New York City, 1896; associated with the American British Consulate Hospital; died in McLean, Va., Aug. 9, aged 84.

Vary, Edwin Phelps Ⓜ Flint, Mich.; University of Michigan School of Medicine, Ann Arbor, 1930; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; veteran of World War II; associated with the McLaren General, Hurley, and St. Joseph hospitals; died Aug. 2, aged 54.

Wadhams, Sanford H. Ⓜ Colonel, U. S. Army, retired, Torrington, Conn.; Yale University School of Medicine, New Haven, 1896; entered the Army in 1900 and retired July 16, 1921; veteran of World War I; fellow of the American College of Surgeons; died in the Charlotte Hungerford Hospital June 14, aged 85.

Watson, Herbert Shirley, Earle, Ark.; University of Tennessee College of Medicine, Memphis, 1916; veteran of World War I; died in the Veterans Administration Hospital in Memphis, Tenn., July 29, aged 67.

Wheeler, James Hartwick Ⓜ Henderson, N. C.; Jefferson Medical College of Philadelphia, 1918; past-president of the Vance County Medical Society; for many years served on the board of education; a director of the Home Building and Loan Association; formerly vice-president of the Commercial and Industrial Bank; past-president of the Henderson Rotary Club; one of the founders and on the staff since its inception, Maria Parham Hospital, where he died July 22, aged 68.

Woodburne, Arthur Wellesley, Tampa, Fla.; University of Western Ontario Faculty of Medicine, London, Ont., Canada, 1898; fellow of the American College of Surgeons; formerly practiced in Entrican and Hastings, Mich.; once a medical missionary in India; died Aug. 1, aged 84.

Zessin, Elmer Theodore Paul Ⓜ Galesburg, Ill.; Chicago College of Medicine and Surgery, 1914; associated with Galesburg Cottage Hospital and the St. Mary's Hospital, where he died July 27, aged 73.

Zonis, Jonathan Ⓜ Boston; Tufts College Medical School, Boston, 1924; member of the American College of Allergists; served on the faculty of his alma mater; associated with the Mount Sinai Hospital, Jewish Memorial Hospital, and the Beth Israel Hospital, where he died July 18, aged 64.

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FOREIGN LETTERS

BRAZIL

Brazilian Trypanosomiasis.—Drs. Jatene and Jacomo, of Uberaba, Minas, studied the problem of transmitting trypanosomiasis through blood transfusion (*Revista goiana de medicina*, March, 1959). They found that the percentage of donors in São Paulo City with a positive Machado Guerreiro reaction (indicative of trypanosomiasis) was higher than that for those with a positive Wassermann test. In the city of Uberaba 15% of the blood donors gave a positive Machado Guerreiro reaction. Some authors have suggested that the blood from donors with positive Machado Guerreiro tests should be sterilized in vitro. Jatene and Jacomo recommended that any blood to be transfused in areas with a high incidence of trypanosomiasis be treated with gentian violet as the only effective preventive measure.

Dr. C. C. Porto, of Belo Horizonte, Minas, in the same issue reported on his electrocardiographic studies of 78 apparently healthy children. Of these, 17 showed a positive Machado Guerreiro reaction, 58 were negative, and in 3 the test was not conclusive. Ventricular premature beats and marked bradycardia in the group with negative Machado Guerreiro reactions made him suspect the possibility of trypanosomiasis and the development of a positive reaction in the future. In the group with a positive reaction, one child had a right bundle-branch block and one had a first degree atrioventricular block. He concluded that these abnormal electrocardiographic findings probably represented the first step in the development of trypanosomiasis and that it is desirable to follow up these patients for a long time.

FRANCE

Marrow Transfusions for Accidental Irradiation.—H. Jammet and co-workers made a further study of the six Yugoslavian scientists who received accidental irradiation and were treated in Paris (*Revue française d'études cliniques et biologiques*, vol. 4, March, 1959). These scientists, five men and one woman, were classified in three categories, according to the degree of irradiation received. One received 1,000 r; four received from 600 to 999 r; and one received 400 r. Warning symptoms such as asthenia, psychic depression, anorexia, nausea, vomiting, sweating, and paresthesia of the upper limbs appeared during the hour after the accident. The least irradiated of these patients had no vomiting; the most irradiated, who later died, besides the symptoms listed above, also had diarrhea.

In the latent period (three weeks) the patients' general condition was comparatively satisfactory in contrast with the course of the hematological, cutaneous, and visceral disorders. Erythema appeared on the first day, accompanied by conjunctivitis. Epilation of the scalp and beard started on the 14th day. Dryness of the skin and subsequent scaling occurred in the subject who received the largest dose. The hemorrhagic disorders were in the forms of epistaxis, gingival bleeding, hematemesis, and, in the woman, menorrhagia. Hematological disorders were immediate leukocytosis (9,000 to 11,000 cells per cubic millimeter) and ensuing lymphopenia. In the latent period there was a gradual decrease in the blood elements. This decrease became more and more marked as it involved first the erythrocytes, then the lymphocytes, thrombocytes, and granulocytes. There was a sharp decrease in lymphocytes during the first five days, with subsequent fluctuations.

The reticulocytes practically disappeared after the first few days, and a reticulocytic crisis occurred at the end of the second week. Then there was a critical period of four to seven weeks, with deterioration of the general condition and clinical findings suggesting typhus except in the subject who received the smallest dose. The nausea recurred, with profuse sweating and diminished diuresis. This critical period was hematologically characterized by an almost total medullary aplasia. The number of neutrophils and of thrombocytes per cubic millimeter fell, respectively, to below 50 and to 30,000. The erythrocyte counts varied from 1,400,000 to 3,000,000.

G. Mathé and co-workers in the same issue reviewed the treatment given to these patients. It started with transfusion of whole blood, platelets, and gamma globulin and administration of antibiotics. In view of the aggravation of the condition, a grafting of embryonic myeloid cells was attempted. The patient who was most heavily irradiated was given a large transfusion of cells from the spleen and liver of a premature infant who had died a few hours after birth. Ten days later his condition deteriorated with the onset of an intestinal syndrome and pain in the right iliac fossa, due to a thrombus. A transfusion of medullary cells from a volunteer donor was then performed. Four days later a rapid increase in blood

The items in these letters are contributed by regular correspondents in the various foreign countries.

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cells was observed, but the intestinal signs were aggravated and the patient's condition was further complicated by anuria and acute renal insufficiency. This patient died from a massive respiratory hemorrhage in spite of an extrarenal dialysis with an artificial kidney.

In view of the aggravation in the hematological condition of the four other heavily irradiated patients, an intravenous injection of marrow from volunteer donors was performed. Each patient received 180 to 300 cc. and a large transfusion of cells. The hematological and clinical conditions took a favorable course. A rapid increase in the reticulocyte, erythrocyte, granulocyte, and platelet counts occurred. The temperature dropped to normal a few days after the marrow was given with a noticeable improvement in the general condition, disappearance of the typhus-like findings, increase in appetite, and gain of weight. Through the study of the blood group phenotypes, by the method of differential agglutination, it was possible to establish the respective percentages of erythrocytes belonging to the donors' phenotypes and of those carrying the patients' own antigens. The curves of the donors' antigens rose to a maximum, then dropped, about one month after the marrow transfusion. The correction of the anemia seemed to be entirely related to the erythrocytic production from the graft.

Some weeks later there were slight oscillations in the granulocytic and thrombocytic curves (the granulocyte count oscillated between 4,000 and 2,000, and the thrombocyte count, between 200,000 and 120,000). This mild disorder was probably due to the replacement, by the patients' own cells, of those produced by the original cells from the donors. The leukocytic and thrombocytic production had had the same origin for one month, i. e., they had originated from the grafted marrow, then they had been destroyed. As their life is much shorter than that of the erythrocytes, the number of leukocytes and thrombocytes replaced must have been much higher than the number of erythrocytes. As to the prognosis, the authors expected hematological fluctuations, spermatogenic abnormalities, and persistence of asthenia for a few months. The probability of induced leukemia or other forms of cancer has increased for these subjects.

GERMANY

Iproniazid for Mental Disturbances.—H. P. Hoheisel (*Medizinische*, no. 12, p. 537, 1959) stated that iproniazid, which was originally developed as a tuberculostatic, aroused the interest of psychiatrists when patients treated with it showed a marked improvement in their contact with reality. Further studies showed the drug to be a potent monoamino-oxydase inhibitor and to cause an accumulation of serotonin and catecholamines in the brain. A series of 74 patients was treated with iproniazid for a long enough period to warrant evaluation. Of these 41 had depressive conditions and 33 had obsessive neuroses. In the depressive group 21 were having their first attack. Results of treatment were surprisingly good in almost all patients. Only three depressive patients were not benefited in spite of treatment being continued for six weeks or more. Side-effects, such as constipation, dryness of the mouth, paresthesias, and exaggerated reflexes, were not observed, although they had been reported by others after treatment with iproniazid. The first noticeable results were seen after only 8 to 12 days. After this period the patients were always relaxed and tractable. After 14 to 20 days of treatment most patients were psychically normal and additional shock or sleep treatment was not required.

In the patients with obsessive neuroses there were more failures. Treatment was started with small gradually increasing doses (50 mg. for five days, then 100 mg. for three or four weeks). Caution is required in iproniazid treatment of patients with renal or hepatic disease and in such patients function tests of the diseased organ are necessary at regular intervals. When an improvement of the psychic condition was manifest, the dose was reduced to 75 mg., then to 50 mg., and eventually to a maintenance dose of 25 mg. for 14 days. The patients should be warned that alcohol intolerance exists during treatment. Side-effects were rare. Three patients developed hepatitis during treatment.

Puerperal Mastitis.—H. Schmidt-Matthiessen (*Landarzt* **35**:437, 1959) stated that reports of mastitis should differentiate between patients delivered in the home and those delivered in the hospital as well as between early and late inflammation of the lactating breast. Figures of the incidence of mastitis are contradictory, but reports of a statistically significant increase are unanimous. It occurs in 0.98 to 4.5% of all puerperal patients irrespective of the place of delivery and it is more frequent in uniparas than in multiparas. The inflammation usually occurs five to nine days post partum. Late mastitis mainly affects women who gave birth in the hospital. The women have returned to their homes in many cases when the first signs of the infection become manifest. This may be the reason why late mastitis usually takes a severer course than early mastitis. The women, having just returned from the hospital, do not consult their doctors at first and therefore come for treatment only in a late stage of the condition.

About 96% of patients with early mastitis can be treated by purely conservative measures. The tendency to abscess formation is negligible. If mastitis following hospital delivery leads to tissue

breakdown, Staphylococcus aureus hemolyticus is found in the pus in 80 to 95% of the patients. These organisms are usually resistant to penicillin, streptomycin, and sulfonamides, and it is necessary to use a broad-spectrum antibiotic. In patients delivered at home Staphylococcus albus is also frequently found. In these patients both organisms are usually sensitive to chemotherapeutic agents, thus rendering conservative treatment much easier. The mechanism of infection occurs when pathogens, which may be found in the nasopharynx of the child from about the fifth day on, enter the breast through small fissures during nursing. Prophylactic measures to be observed are good ventilation of rooms, hygienic care of the nipples, wearing of face masks for mothers and nursing personnel, and disinfection of hands.

In its early stage the infection can often be controlled by x-ray treatment. After pumping the breast 80 to 100 r are given and this treatment, if necessary, may be repeated on the following day. If the symptoms have disappeared by the second day, the breast is emptied again on the third day, and nursing carefully resumed on the fourth day. Patients with late mastitis are given antibiotics in addition. Should the local symptoms not subside, incision and drainage is necessary. The child is not nursed then because of the danger of transmitting the infection with the milk. Phenobarbital, diethyldioxystilbene-dipropionate, and estrin, together with restriction of fluid intake, usually make it possible to control the initial milk flow.

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Spermiogenetic Infantilism.—O. Hornstein (*Klin. Wchnschr.* **37**:105, 1959) stated that partial insufficiency of the anterior lobe of the hypophysis produces a variety of symptoms, according to the degree and time of dysfunction. The gonadotropic hormones are usually lacking at first. Deficiency of both gonadotropic factors, interstitial cell stimulating hormone and follicle stimulating hormone (ICSH and FSH), as a rule, occur simultaneously. This gives rise to the so-called hypogonadotropic hypogenitalism. Clinical observations are, however, suggestive of an isolated deficiency of FSH, too, which causes a syndrome termed "fertile eunuchoidism," since in it true spermiogenesis is preserved while secondary sex characteristics are not developed. The opposite condition—isolated deficiency of ICSH—has not been observed.

The following case, therefore, deserves special attention: A 32-year-old man came for consultation because his marriage had been sterile. He was of somewhat hypovirile but not eunuchoid build. His voice changed at 20 and at that time he first shaved. He married at 26 years of age. His libido was normal. Examination revealed a light beard growth and feminine distribution of pubic hair. His testes were only cherry-size and soft. No sperms were present in the spermiogram. Gonadotropin and 17-ketosteroid levels were low. A testicular biopsy revealed, apart from a well-developed interstitium with clusters of Leydig's cells, only tubules of infantile appearance with indistinct cellular structure, no sperm cells or mature precursors. This appeared to be a case of dissociated secondary hypogenitalism, which may be explained by the absence of FSH stimulation of the tubules since puberty. In this case it represents the opposite condition to "fertile eunuchoidism," the secondary sex characteristics having been developed by the stimulation of interstitial cells, but spermiogenesis not having been initiated because of FSH deficiency.

Malformations in Newborn Infants.—H. Oster (*Kinderärztl. Praxis* **27**:28, 1959) stressed the importance of studying the incidence of malformations of newborn infants in the last two decades in order to determine whether as a result of atomic explosions the incidence of malformations and anomalies in neonates has been increasing. The comprehensive material presented by the author showed no increase in the incidence of malformations for the period 1939 to 1953 compared with the period 1954 to 1958.

INDIA

Chlorpromazine for Tetanus.—B. J. Vakil and coworkers (*Journal of Association of Physicians of India*, vol. 7, July, 1959) treated 259 patients who had tetanus with chlorpromazine in addition to the routine standard treatment. Chlorpromazine was given only to those whose spasms were severe, frequent, and uncontrollable by the routine treatment. Another 81 patients with mild symptoms were controlled with sedatives only. Another group of patients admitted prior to these, and who received only the usual treatment, served as controls. The standard treatment consisted of local treatment of the wound and administration of the antitoxins, antibiotics, and sedatives. Cortisone or its derivatives were occasionally used to relieve allergy or anaphylaxis and mephenesin was sometimes given to facilitate feeding. Tracheotomy was performed on three patients. The dose of chlorpromazine was adjusted according to requirements but a total dose of 1 Gm. in 24 hours was seldom exceeded. The method of choice for administering this drug was the intravenous drip. The largest daily dose used was 1.5 Gm. in an adult. The longest period of administration was 12 days, with the drug being discontinued when the spasms were reduced in intensity and could be controlled by sedatives only.

The case fatality rate with this treatment was 25% while in the control group it was 35%. The authors found the results with chlorpromazine grat-

ifying in the control of spasms and rigidity. Hypertonia and rigidity were reduced in most patients but rarely were abolished completely. Symptoms of a few patients were, however, completely resistant to the drug even in large doses. Thus, of the 259 patients, 221 showed a favorable response, and 15 died of glottic spasms while the drip was being administered. Neonates and children responded poorly to the drug. The patients so treated were on the whole, relaxed, cheerful, and conscious and feeding was much simpler as most could be fed orally. Coma and respiratory depressions were not serious problems as they were in the control group. No major toxic reaction occurred. In this series eight patients had cephalic tetanus, which is a type well known for its poor prognosis. With chlorpromazine seven of the eight survived. None of the neonates in the control series survived while in the present study 2 of 17 were saved.

Serum Amylase in Mumps.—N. P. Misra (*Journal of the Association of Physicians of India*, vol. 7, July, 1959) determined the serum amylase level in 17 patients with mumps. The normal range was determined in 100 normal subjects. The level was elevated in all the patients. The highest level was observed in the first week of illness except in one patient. In most patients, the level returned to normal by the end of the second week, coinciding with the clinical remission of the disease. A close relation was noticed between the severity of the clinical condition and the serum amylase level. It was also highest in patients whose swelling was most prominent and higher in those with bilateral than in those with unilateral involvement. Development of orchitis, unilateral or bilateral, did not influence the level. The serum amlyase level elevation in patients with mumps was thus a function of the disease associated with parotitis alone. This finding may be used to differentiate mumps from swelling of the face due to other causes such as an impacted molar, bull-neck following diphtheria, lymphadenitis, cellulitis, and fracture-dislocation of the mandible.

C-Reactive Proteins.—P. M. Chaphekar (*Journal of Postgraduate Medicine*, vol. 5, July, 1959) stated that the C-reactive protein (CRP) level reflects the activity of pneumococcic pneumonia and it disappears promptly when the progress of the disease is arrested. The test is of greater help in assessing prognosis than in making a diagnosis. The author studied the CRP level in diseases of the liver to find out whether it would help in judging the activity of the destructive and inflammatory processes associated with viral hepatitis and cirrhosis. Estimations of the sedimentation rate were carried out simultaneously. In 31 normal subjects of both sexes from 1 to 40 years old the test for CRP was uniformly negative while the sedimentation rate ranged from 8 to 30 mm. In seven patients with full-term pregnancy with no complications, the test was weakly positive in two and negative in five and the sedimentation rate varied from 35 to 50 mm. Blood collected at autopsy from accidental death in four patients was also negative for CRP.

Of 42 patients with infectious hepatitis, 16 gave positive reactions. Of 26 patients with cirrhosis of the liver in whom secondary infection was ruled out 18 gave the reaction for CRP. In two patients with primary and one with secondary carcinoma of the liver blood collected at autopsy was found to be strongly positive for CRP. The patients with infectious hepatitis who gave positive tests for CRP were more severely ill and the case fatality rate in these patients was about 10 times higher than in those with negative tests. Similarly patients with cirrhosis who had positive tests were in worse condition than those with negative results. Biopsy specimens from these patients were suggestive of a smoldering necrosis, fibrosis, and mononuclear infiltration.

The electrophoretic pattern showed a greater fall in total plasma proteins in those with positive as compared to those with negative tests and also in albumin, alpha-1 globulin, beta globulin, and gamma globulin fractions, but the fall in alpha-2 and gamma globulin fractions was less. Other diseases besides liver diseases were also studied for CRP. Positive tests were observed in patients with rheumatic pericarditis, myeloid leukemia, multiple myeloma, Hodgkin's disease, rheumatoid arthritis, visceral leishmaniasis, and hemolytic anemia. The test was strongly positive in those with visceral leishmaniasis but became negative after treatment. Although the test for CRP has the same significance as the sedimentation rate, the author believed it to be superior as it is simpler and is more uniformly negative in normal subjects. This is especially helpful in normal pregnancy when the sedimentation rate goes up while the CRP test is negative or weakly positive. The test may serve as a valuable adjunct to liver function tests and to differentiate postnecrotic cirrhosis from cirrhosis following fatty change.

Ascorbic Acid Levels and Influenza.—P. S. Vaishwanar and co-workers (*Indian Journal of Medical Sciences*, vol. 13, July, 1959) believed the estimation of the ascorbic acid level in whole blood to be of greater significance than that of serum or plasma in assessing nutritional status as the plasma value represents only the immediate nutritive or metabolic level depending on the recent dietary intake. The authors studied the blood ascorbic acid level in 66 children, in 28 of whom the estimations were made first in March, 1957, and again in July, 1957, immediately after an influenza epidemic. In the other 38 only single estimations were made after the epidemic in August, 1957. The figures for blood

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ascorbic acid in children with no history of influenza were higher than those who had had the disease. The ratio in some was almost 2:1. In those for whom figures before the epidemic were available it was seen that the difference in the level in those with and without the history of influenza was the result, and not the cause, of infection. If the ascorbic acid level played any part in determining resistance to infection, it must have been small.

SPAIN

Protection Against Ionizing Radiations.—At the First National Medical Congress of the Spanish Red Cross held in Madrid in May the following conclusions were reached: It is necessary to inform the public about the dangers of radiologic pelvimetry and of serial intestinal roentgenography in pregnant women and to limit the amount of irradiation to all patients. All persons who work with ionizing radiations must be examined periodically, and temporarily removed from their tasks if their exposure to radiation exceeds the limits of safety. The public must be reassured that nuclear energy plants have developed complex systems of protection not only for the personnel working in those plants but also for the surrounding areas and that such plants do not represent a danger for the adjoining populated areas if the protective systems are adequate and properly operated.

Furthermore, the mobile installations of nuclear energy in submarines, and the portable army installations, or those in areas of difficult supply of usual fuel should not offer any danger to the waters where they navigate, the ports where they anchor, or the zones where they are stationed. The Red Cross should provide specialized teams and personnel to provide adequate care to any victims of accidents that might occur in isotope plants or laboratories. The Red Cross should also organize specialized aid units throughout the nation, in collaboration with civil defense personnel. All members of these units should be able to give first aid to victims of blast, thermal, and irradiation injuries caused by an atomic explosion.

Interauricular Septal Defects.—At the same meeting, Dr. Enrique Garcia Ortiz and co-workers presented a study of 40 patients with interauricular septal defects. They found that cyanosis is always associated with pulmonary arterial hypertension and with an increase in pulmonary resistance. It is rarely observed in young persons without circulatory decompensation, and it is always a consequence of massive arteriovenous shunt. In adults cyanosis appears in patients with cardiac insufficiency, complete arrhythmia, and an enlarged heart. Cardiac insufficiency is characteristic of interauricular septal defects. Sometimes an arteriovenous shunt persists and the arterial hypertension is inconstant. In this type of cardiopathy the elevation of pressures in the refilling of the left ventricle does not necessarily cause myocardial failure.

The radiologic changes in the pulmonary arterial tree continue to be a reliable sign of interauricular septal defects. The heart is enlarged, especially in the forms associated with great pulmonary deficit and marked arterial hypertension. The electrocardiographic changes reveal acquired abnormalities in which a complete bundle-branch block represents the last stage which may regress after the surgical closing of the septal defect. The hemodynamic examination shows, in most patients, a normal venous saturation. In more than half of the patients mixed shunts are observed. The curves of pressures obtained simultaneously in both auricles indicated that the mechanism of pressures at the auricular level was not sufficient to explain the direction of the shunts. In patients with an increase in the pulmonary deficit, pulmonary arterial hypertension is slight or moderate, but in those with an increase in arterial resistance it is severe.

The treatment consists of an open repair with use of hypothermia or prostigmin. This treatment should give satisfactory results in cases of patent foramen ovale, ostium secundum, and simple ostium primum, since the time limit is sufficient for closing these three types of septal defects. In a patient in whom there was drainage of the abnormal pulmonary veins, it was possible to divert the flow from the septum and to close the defect with complete success. The authors believe that, in patients with a common atrioventricular canal, hypothermia should not be applied but the heart-lung machine should be used.

SWEDEN

Hydrocortisone During Operation.—B. Aldman and co-workers (*Svenska läkartidningen*, June 26, 1959) gave hydrocortisone to patients during operation. They classified these patients as acute operative emergencies or elective cases. For the first category hydrocortisone was given by intravenous drip or injection in doses of 100 mg., a total of 100 to 300 mg. being given during the operation, and 100 mg. by intramuscular injection morning and evening for two days after the operation. A further 100 mg. was given by intravenous injection if a postoperative fall of the blood pressure threatened. For the elective cases 100 mg. was given by intramuscular injection for two days before operation or on the morning of the day of operation. During the operation 100 to 300 mg. was given by intravenous drip or injection. During each of the first postoperative days 100 mg. was given twice by intramuscular injection. This treatment did not interfere with the

healing of wounds and it may have improved the operative prognosis, particularly for those threatened by flagging of the suprarenal system.

Tobacco Addiction.—In 1955 Dr. B. Ejrup (*Svenska läkartidningen*, July 3, 1959) started giving injections of lobelin hydrochloride to heavy smokers. By the end of 1957 he found that 93% of these patients got some benefit from the injections. Early in 1958 the first polyclinic for the weaning of heavy smokers was opened, and a little later there were six such clinics. In cooperation with various organizations combating tuberculosis and cancer, Ejrup sought to turn these clinics into research centers. He has had to rid the public of the notion that his treatment is based on a single drug, his ambition being to devise a system or series of simple measures suitable for general application to the control of the smoking habit. At the Danish equivalents of the Swedish polyclinics the patients pay for each drug injected, but in Sweden no separate charge is made for the drugs as it is desirable to feel free to vary the drugs or to give placebos for the sake of comparison. About 150 physicians cooperate with the polyclinics in compiling the observations made, and in Stockholm alone there are about 2,000 smokers whose reactions have been recorded. From his experience with the staffs of two industrial concerns, Ejrup estimated that Sweden, with a population of 7 million, has at least 150,000 nationals in need of his polyclinics. The commercial interests linked to the sale of tobacco need not, in his opinion, be alarmed about his polyclinics which are not waging war on tobacco in general, but only on the abuse of it by a small fraction of the population.

Corneal Opacities from Chloroquine.—According to Dr. O. Gabinus and co-workers (*Svenska läkartidningen*, July 10, 1959) since January, 1958, chloroquine has been given at the Jönköping General Hospital to patients with rheumatoid arthritis and other collagen diseases, the usual maintenance dosage being 250 mg. daily after twice to four times this amount in the first few weeks of treatment. Side-effects were on the whole negligible, but of the 19 patients examined with a corneal microscope 8 showed epithelial and subepithelial deposits on the lower half of the cornea. These diffuse opacities were homogeneous with the exception of those in one patient in whom they were slightly granular. No other abnormalities of the eyes were detected.

UNITED KINGDOM

Koilonychia.—Koilonychia is generally attributed to iron deficiency. Jalili and Al-Kassab (*Lancet* **2**:108, 1959) investigated the incidence of this disease in patients with severe anemia, but they could find no correlation between the severity of the anemia and the occurrence of koilonychia. There was no statistical difference between the hemoglobin levels of patients with and without the condition. The nails were not deformed in some patients with a hemoglobin level of 1.5 to 3 Gm. per 100 ml. It was therefore concluded that iron deficiency alone does not explain the changes in the nails. In view of the poor protein intake of the patients and the fact that cystine is an important constituent of nails and is responsible for the crosslinkage in the polypeptide chains which contributes to the strength of the protein structure, cystine, arginine, and histidine levels in the fingernails of the patients were determined. The cystine in the nails of 29 normal subjects averaged 8.12%. It was independent of sex and social status. The cystine content of the nails of patients with koilonychia was much lower, averaging 2.54%. It was also low in patients with anemia without koilonychia, the average being 6.32%. The cystine content of the nails of two patients with koilonychia rose greatly and became more than double the initial value after increasing the protein content of the diet. The histidine and arginine content of the nails in koilonychia was within normal limits. According to Jalili and Al-Kassab a deficiency of sulfur-containing amino acids is a factor in the pathogenesis of koilonychia.

Hemoptysis due to Endometriosis.—Endometriosis is occasionally found in extra genital situations, such as the intestine, peritoneum, bladder and, rarely, the lung. Fleishman and Davidson describe the occurrence of hemoptysis in a woman, who at first was thought to be suffering from pulmonary tuberculosis, although a chest film, bronchoscopy, and bronchography did not reveal a tuberculous lesion (*Lancet* **2**:88, 1959). When it was discovered that hemoptysis regularly coincided with the onset of menstruation a diagnosis of pulmonary endometriosis was made. The hemorrhage diminished, although it did not stop, when 25 mg. of testosterone dipropionate was given a few days before the expected period. When the hormone was stopped the hemorrhage from the lung was severe. Radiographs and tomograms taken between the menstrual periods were normal, but when taken the day before the expected date of menstruation a small area of infiltration was observed in the left upper lobe on two occasions. A lobectomy was planned but was not done as the hemoptysis diminished in severity and eventually stopped. Although histological proof was lacking it was believed that the lung lesion was endometriosis. The eventual cessation of hemoptysis despite continued normal menstruation and the inconstant radiologic appearances were attributed to the gradual sequestration of the ectopic endometrium via the draining bronchus.

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MISCELLANY

MEDICINE AND AUTOMOBILE RACING

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Automobile racing has been known in the United States for years. From the old Vanderbilt Cup races on the Motor Parkway of Long Island, N. Y., in the early 1900's, racing has grown to a major sport. Before World War II crowds were drawn to Indianapolis, to hundreds of fairground dirt tracks, and to see the mighty midgets race on the 1/10-mile ovals throughout the many cities of our country. The daredevils of the 20's and 30's drove without restrictions or regard for personal safety. Death claimed many from their ranks in those days, from either faulty machinery, faulty road surfaces, or questionable driver qualifications. Medicine was seldom mentioned, in the heyday of dirt track racing.

Soon after World War II, small, racy, noisy sports cars began to make their appearance in the United States. The MG was the first to catch the fancy of sports-minded Americans. With the first invasion of foreign cars came a new sport—road racing. Europe had known road racing for years and European cars were built for this type of driving. Instead of in an enclosed oval, where speed was essential for winning, road racing took place on country lanes and city thoroughfares. This type of driving required more dexterity and stronger gear boxes than the ordinary oval track racing would ever require of a car. A road course might run from border to border of a country, such as in the Mexican Road Race, or follow a twisting, turning, dangerous course through a city, as in the yearly race at Monaco on the Mediterranean coast. The road races of Europe have been run on public roads closed to traffic on the day of the race.

The first attempts to establish road racing in the United States were at Watkins Glen in upstate New York and Bridgehampton, L. I. These races whetted the American appetite for fun and thrills and a new sport was born.

Problems quickly arose, however, and indignant townspeople forced the termination of racing on public roads. Racing quickly moved to airports, where spectator control could be enforced. Gen. Curtis Le May was instrumental in establishing many fine airport racecourses at Army air bases throughout the country. Disgruntled GI's and vote-happy congressmen soon put a stop to racing on government property, however, even though the proceeds from the races were filling the enlisted men's club treasuries. This handicap was in turn overcome by the establishment of privately owned, hard-surface racecourses across the country, from Limerock, Conn., down to Danville, Va., and out to Riverside, Calif.

Medical observers, some of whom are drivers themselves, became increasingly aware of the need for safety standards on American racecourses. Physicians began to investigate accidents. It soon became apparent that regulations governing racing would have to be enforced. Even though the driver considered it "sissy" or "uncomfortable," he would have to abide by the rules, if he wished to drive. The Sports Car Club of America (SCCA) became the governing organization for most amateur races in America. The directors and officers were men of foresight. Accidents caused public concern; death is certainly a cause for indignation. A medical advisory committee was established within the organization. This committee was given authority to enforce safety regulations at all Sports Car Club races.

The first directives were met with varied reactions, but the doctors were patient and soon noted compliance with all their regulations. As racing picked up in momentum, so did research. Dr. George G. Snively of California upset the manufacturers of helmets by condemning one helmet after another. With the aid of research departments at different universities, he could determine the resistance to stress of the materials used in making racing helmets. Helmets of drivers involved in accidents were also studied and defects noted. After many months of impartial investigation he made his recommendations, and they have become regulations for drivers on the SCCA racecourses today. Of course, manufacturers were indignant, but some were grateful and improved their products until they, too, were acceptable.

Along with the helmets went the problem of visors or goggles. Many types are on the market and there are as many adherents to each of the different designs. Recently the "blister" type of visor has been introduced and has been found satisfactory, if made of the right type of plastic and worn properly. The acetate and butyrate plastics are the best, since they do not shatter and will not leave jagged, pointed edges to cut facial tissues. The nitrates will give the same protection but are highly inflammable and thus are not used. These plastics are soft and scratch easily, compared to acrylic plastic, but this only necessitates care when they are not in use. Visors or goggles with metal supports are not recommended. The California Sports Car Club has outlawed all goggles not set in rubber. Any visual protection made of glass is also discouraged. Eyeglasses made of shatterproof plastic are now on the market, and they have been recommended for drivers who must wear glasses.

Most European drivers will not wear a safety belt. They feel they have less chance of getting hurt if they are thrown clear of the car instead of riding into a crash stop. American drivers feel they have

Medical Director of Virginia International Raceway; member, Medical Staff, Grand Prix Races, Sebring, Fla.

less chance of injury if they remain within the car. This has caused much discussion, and no definite solution has been found; but the Sports Car Club of America insists on safety belts. They have based their regulations on research work done by scientists at Cornell University and on investigation of accidents. It has become a known fact that fewer Americans would have been killed in the past years if they had not been thrown from their cars during accidents. You are safer within the car. When a crash is followed by fire, the Europeans might be right; but the danger of fire is small compared to the possibility of getting crushed by a rolling car or a following car. Most medical men and automotive engineers agree that safety belts are imperative.

Safety devices can also cause injury, however. The width of the belt, where it is anchored to the car, and the type of buckle are all-important. A 3-in. width is recommended for racing and not less than a 2-in. width should be used in passenger cars. A thin belt could cause undue trauma to abdominal and pelvic organs after a severe impact. The belt should rest not across the thighs but at a 45-degree angle across the pelvic bone. The belt should be fastened to the frame of the car and not just to the seat, since the seat can easily tear loose and throw its occupant into the air on the first roll of the car. Even with a belt, men have had their faces injured by hitting the steering wheel. The shoulder harness would prevent this and would also prevent many whiplash injuries to the neck. It has recently been recommended by many safety experts that a shoulder harness plus a seat belt should be worn by drivers at all times. Buckles on belts can be annoying, especially when they lock and the driver cannot release the belt after an accident. The airline type of locking buckle is acceptable, but attempts are being made to improve this.

The roll bar has caused many a "he-man" to sneer, yet today one will not see a sports car, stock car, or any professional racing car without this simple protection. A bar of sufficient strength behind the driver's head, anchored to the car's frame, is lifesaving. Hard tops on cars can crush easily, and the roll bar is just as important to the hardtop car as it is to the convertible. Some American manufacturers are considering incorporating a roll bar into the windshield support of every car.

Fires are infrequent but a definite problem. Drivers are advised to wear flame-resistant coveralls which are fitted tight around the neck, wrist, and ankle. They should wear driving gloves to protect the hands and adequate shoes to protect the feet from harm. Clothing is easily rendered flame-resistant by immersion in a boric solution. Each automobile must have a fire extinguisher in the cockpit before it can be given approval to race.

Inspection of automobiles does not come under medical problems, but it has become an important part of racing. Before a practice run can be made on a course, each automobile is gone over by a qualified mechanic. If the brakes, lights, and condition of the tires are unsafe for fast-speed driving, the automobile is not permitted to run. This protects the driver as well as others on the course who might become involved in an accident caused by faulty equipment. Along with automobile inspection goes driver inspection. Before every endurance race a driver must submit to a physical examination. Heart, lungs, and eyes are all checked. One or two drivers are always weeded out by these examinations. As far as sprint racing is concerned, all SCCA drivers must receive a yearly physical examination. The background of the driver, with regard to epilepsy, insulin reaction, heart disease, fainting, and any disease that might influence reflexes, is investigated. The physical examination must be completed with care and attention to detail, including the eye examination.

Physicians have also become aware of the psychologically unfit driver. "That man will kill himself within a year," is a remark frequently heard at a racecourse. Since these drivers often do kill themselves, it is up to the physicians to try to weed out these drivers before they do harm to themselves or others. Some drivers flirt with death on every turn; other drivers have superior reflexes and can drive the car to the limit of its capacity. It is difficult to disqualify a man because he drives fast, but the medical recommendations are being accepted when most consultants believe a driver is psychologically unfit to race. A driver has an opportunity to appeal to a board of directors and can call his own physician in his defense. Physicians are doing their best to protect the majority from a reckless few. A psychological test is under study that may help to eliminate unfit racing drivers as well as unqualified Sunday drivers on our local highways.

Many believe the physicians interested in racing and sports-car activities are eccentric and are wasting precious time. Little publicity has been given the medical men working on improving highway safety through their racecourse laboratories. Dr. Snively's work on helmets has caused the California highway police to seek recommended head protection for their motorcycle force. Safety belts first used in racing have been advised for all passenger cars. Tires tested and punished at races are now on our everyday cars. Brakes, which were most inadequate for our heavy, high-powered passenger cars, have recently been improved by American manufacturers but only after much pressure from medical men and engineers who realized that power needs a halter. The work being done by the Cornell group and Dr. Miles O'Brien at Limerock, Conn., will soon influence every roadway constructed in America. Dr. O'Brien is conducting a series of tests for night driving and night blindness.

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His report on these studies will be concerned with the effects of lighting and the causes of nighttime accidents.

The racecourse itself is not the physician's concern, but track officials are now seeking and listening to the medical directors who can foresee a dangerous situation. Doctors interested in trauma have developed insights into the causes of injury. Drivers and officials have finally realized that the course physicians are primarily interested in the health and safety of the drivers and not in speed records.

The American Association for Automotive Medicine was formed by a small group of physicians at the Sebring International Races three years ago. This group has grown to include over 40 members from coast to coast. The primary aim of the organization is to reduce accidents and injuries on racecourses. It is hoped that through their work with high-speed vehicles they will be able to persuade manufacturers and automotive engineers to improve safety features on our roads and in our family automobiles.

713 Hancock St.

MEDICAL FILM REVIEWS

Management of Burns, Part I: Supportive Care (PMF 5318); Management of Burns, Part II: Local Care (PMF 5319): 16 mm., color, sound, showing time: part I, 17 minutes; part II, 14 minutes. Produced in 1958 by the Department of the Army. Procurable on loan from the Surgeon of the Army Area in which the requestor resides or on purchase from United World Films Inc., 1445 Park Ave., New York 29.

Part 1 of this film covers the diagnosis, care, and treatment of patients suffering from burn injuries and points out that early supportive care is vital for recovery. Initial hospital procedures for treatment of burns are outlined, with stress on accurate appraisal of injury; sedation; establishment of a venous life line; requirement for tracheotomy; maintenance of patient's urinary output; planned fluid therapy; and use of hematocrit to determine relative amounts of plasma and corpuscles in the blood. The importance of building up the patient's morale for ultimate recovery is emphasized. In part 2, the essentials of supportive care are reviewed. Then, the steps of local care are presented, including cleansing of the wound; débridement of the skin; treatment with occlusive dressing; air treatment; and skin grafting. These are excellent films and the procedures used are those that are generally accepted as most satisfactory for this kind of injury. The films are highly recommended for physicians, medical students, and all hospital personnel who take part in the treatment of the burned patient, including nurses, hospital technicians, and aids. It would also be of value to people who have had advanced training in first aid and who may be involved in the care of mass casualties.

Help for Young Hearts: 16 mm., black and white, sound, showing time 14 minutes. Produced in 1958 by Potomac Film Producers for and procurable on loan from American Heart Association Film Library, 267 W. 25th St., New York 1.

The central theme of this film is that a child who has been held back by rheumatic heart disease can, with proper medical supervision and vocational guidance, grow up to normal living and become a useful member of the community. It emphasizes the part medical prophylaxis and vocational counseling can play in helping young people whose hearts have been damaged by rheumatic fever and also shows how parents are learning to protect children who have had rheumatic fever against recurrence of the disease. It points out that parents of the child with rheumatic fever may obtain information about protective drugs from their physicians or through local heart associations. A key point in this film is that it emphasizes what these children can do rather than what they cannot do and shows that the children can assume some responsibility of their own with regard to such matters as taking their medicine. This film is recommended especially for parent groups and for the training of professional people who will be working with children, such as physicians, social workers, teachers, nurses, physical therapists, and youth leaders.

Mouth to Mouth Resuscitation for Respiratory Emergencies: 16 mm., color, sound, showing time 18 minutes. Prepared in 1958 by and procurable on loan from Archer S. Gordon, M.D., 4614 Sunset Blvd., Los Angeles 27.

This film details the physiological requirements for effective artificial respiration and outlines the experimental and practical background of the development of mouth-to-mouth resuscitation. Regular and slow motion views depict the preferred techniques for mouth-to-mouth and mouth-to-nose resuscitation for children and adults. The use of an airway and mask are also demonstrated. The necessity for speed, maintenance of a clear airway, and adequate ventilation are emphasized. This film covers the subject of resuscitation without presenting large amounts of detail and in addition to the mouth-to-mouth method demonstrates three manipulative methods which have been effective. The photography is magnificent, the narration is clear, the action is efficient, and the film will be immediately intelligible and instructive to audiences of any age. It will appeal to physicians and is also recommended for showing to nonprofessional groups.

Total Hysterectomy: 16 mm., color, sound, showing time 27 minutes. Prepared by Somers H. Sturgis, M.D., Boston. Produced in 1958 by Sturgis Grant Productions, New York. Procurable on loan from Winthrop Laboratories, 1450 Broadway, New York.

The purpose of this film is to depict the author's technique for total hysterectomy in the manner in which it is taught to surgical residents at the Peter Bent Brigham Hospital. It follows the steps of the operation, including a preliminary dilatation and curettage, and contains diagrams to clarify surgical features as well as photomicrographs to document the case which is presented. In this film, the operation was performed on a 33-year-old mother of three children who was found to have a positive vaginal smear on a routine medical checkup. Cervical biopsy specimens showed carcinoma in situ. The patient first is operated on from below for a curettage and examination under anesthesia. Then she is placed, recumbent, into a modified Trendelenburg position, and total hysterectomy is performed through a transverse incision well superior to the pubic hairline. The color and photography of this film are excellent and it is recommended for physicians and medical students.

A Three-Stage Repair of Hypospadias: 16 mm., color, silent, showing time 13 minutes. Prepared in 1958 by and procurable on loan from S. Harris Johnson, III, M.D., and Matthew Marshall Jr., M.D., 509 Peoples E. E. Bldg., Pittsburgh 6.

This film demonstrates a three-stage operative technique for the repair of hypospadias. The method of repair, while based on techniques previously described, has been devised by the authors. There is reconstruction of the urethra from skin not only from the penis but also the scrotum. Construction of straight corpora cavernosa, a large-caliber urethra, and a meatus in a relatively normal position have been accomplished with a low incidence of relatively minor complications. The photography is excellent, and one can easily follow the operative procedure for this special technique. Since it is a very technical film and skips about rapidly, only urologists and plastic surgeons would be able to follow this technique intelligently, even with the captions that explain it. This film should be of special interest to urologists, plastic surgeons, and possibly some general surgeons who do certain types of plastic surgery. It is also recommended for residents in urology and plastic surgery.

Air Force Industrial Medicine in Action: 16 mm., color, sound, showing time 20 minutes. Produced in 1958 by the Department of the Air Force. Procurable on loan from Armed Forces Film Library Center, St. Louis 23.

This film illustrates the investigation and solution in an Air Force manufacturing establishment of an occupational health problem which attracted attention by an unusually high rate of absence due to illness in workers who performed a particular operation. It presents the philosophy that industrial medicine should be concerned primarily with prevention. While a more illustrative occupational health problem might have been selected, the film does show clearly the "team" approach necessary in occupational health, the plant physician, the industrial hygienist, the industrial nurse, and the supervisory personnel all being shown as contributing their particular skills to the solution of the problem. The photography is good, the production technique adequate, and the sound recording effective. This film is highly recommended for industrial physicians and others interested in industrial health.

The following films were produced in 1957 by and are procurable on long-term lease or purchase from Walt Disney Productions, 500 S. Buena Vista, Burbank, Calif. All are in color and sound and the showing time is 8 minutes each.

I'm No Fool as a Pedestrian: This film presents, through an animated cartoon with Jiminy Cricket as the moderator, the basic rules of safety for the pedestrian. The historical background of man from the stone ages up to modern times and the development of the automobile are portrayed. The film compares "you" as a safe individual and a "fool." It emphasizes alertness and the right and wrong safety measures to be taken by a pedestrian.

I'm No Fool Having Fun: The basic rules of safety and having fun are presented by Jiminy Cricket. The historical background presents the fact that, with the development of the machine and the 40-hour week, man began having more leisure time and, therefore, having fun. This film presents the basic rules of safety for such sports as hiking, swimming, skating, bicycling, and boating.

I'm No Fool in Water: The historical background of man and his use of water for recreational purposes is portrayed in the beginning of this film. It compares "you" as a safe individual and as a "fool" in the water. The film presents the right and wrong places for swimming and instills respect for water.

I'm No Fool with a Bicycle: This film shows the right and wrong ways of riding a bicycle and portrays the historical background of the bicycle. Jiminy Cricket conducts a contest between a "good boy" and an "ordinary fool"; the latter's disregard for safety leads to disaster.

I'm No Fool with Fire: This film illustrates the basic rules of safety with regard to fire as Jiminy Cricket points out the use and control of fire and the importance of fire prevention.

These are excellent films for children. They are logical in their presentation and very well organized. They will hold any child's interest and teach him the basic rules of safety in the situations shown.

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V. 1

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Analysis of the Progress and Results Obtained in 134 Cases of Thyrotoxicosis with Radioactive Iodine (I^{131}). R. J. Soto, I. B. Rozados, O. J. Degrossi, F. A. Diez and others. Semana méd. 66:653-669 (May 21) 1959 (In Spanish) [Buenos Aires].

A group of 200 patients with hyperthyroidism was treated with I^{131}, which is at present the preferred iodine radioisotope for the treatment of thyrotoxicosis. This report covers the results obtained in 134 patients whose recovery or improvement was considered permanent. The majority of them (75%) were women, and the ages varied from 15 to 75 years, with the highest frequencies in the 40-55-year age bracket. Most patients were under 45. The group was classified into five subgroups according to the characteristics of the disease, namely, diffuse toxic goiter, nodular toxic goiter, thyrotoxicosis without goiter, cardiothyrotoxicosis, and recurrent thyrotoxicosis after surgical therapy.

The dose of radioisotope was established on the basis of the size of the thyroid (evaluated by palpation), and each patient received 200 microcuries per gram of the glandular weight, except for the group with recidivation. In the latter group the dose was 300 microcuries per gram. To avoid the induction of hypothyroidism, the maximal dose was kept at 20,000 microcuries for those with nodular goiter and at 15,000 for those with diffuse goiter. The median dose applied was 14,799 microcuries; the highest requirements were those of the patients with nodular goiter and with cardiothyrotoxicosis. The radioisotope was given orally while the subjects were fasting and after the blood cholesterol level, basal metabolism, and radioactive uptake had been checked. These tests were repeated every 2 or 3, 4 to 6, and 8 to 12 months after administration of I^{131}.

During the course of the treatment, 14 patients had temporary hypothyroidism with spontaneous recovery. Twenty-eight suffered slight loss of hair, and 16 developed a pain in the neck, with exacerbation of the thyrotoxicosis for a few days. Nineteen patients developed atrial fibrillation, which disappeared in 11 of of them. Permanent recovery was obtained in 127 patients; 5 became hypothyroid; and 2 abandoned the treatment. The time necessary for recovery varied between 3 and 4 months in the groups with diffuse, or without, goiter; the nodular forms required therapy for a longer period. The ophthalmic complication improved in 81 patients and became stationary in the others. These results were obtained with one dose of I^{131} in 98 patients, with 2 doses in 28, and with 3 doses in 5; only one patient required 4 doses.

Dietary Linoleic Acid and Linoleate: Effects in Diabetic and Nondiabetic Subjects With and Without Vascular Disease. L. W. Kinsell, G. D. Michaels, G. Walker and others. Diabetes 8:179-188 (May-June) 1959 [New York].

The authors discuss the relationship of dietary linoleic acid to a variety of plasma lipids in diabetic and nondiabetic subjects, many of whom had significant vascular disease. Some studies were carried out in ambulatory patients on semiconstant dietary intake, while others were carried out in patients on the metabolic ward receiving quantitatively constant dietary intake. The data presented in this paper appear to establish that linoleic acid administered either as purified ethyl ester or as naturally occurring fat, in sufficient quantity, in properly constructed diets, will reduce plasma lipids. Many vegetable fats lower levels of plasma cholesterol and other plasma lipids, but linoleic acid appears to be the constituent of these fats which is responsible for such effects. Generally speaking, the greater the amount of saturated fat in the diet, the greater the amount of linoleic acid required to produce a desirable lowering of plasma lipid levels. Because of major individual differences in response in patients with vascular pathology, lipidoses, etc., it is impossible to set up a ratio of relationships between dietary saturated and unsaturated fatty acids which will apply generally. In some diabetic and nondiabetic patients with vascular disease, subjective and objective improvement has been noted in association with the intake of diets containing large amounts of linoleate. It is still too early to state positively that such improvement is related directly to the diets employed. The fatty acid composition of the diet specifically influences the composition of the plasma cholesterol esters. High linoleate intake results in markedly increased plas-

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ma cholesterol linoleate, and high oleate intake results in markedly increased plasma cholesterol oleate.

Influenzal Pituitary Depression. J. N. Mickerson. Lancet 1:1118-1121 (May 30) 1959 [London].

Debility, involving not only bodily discomfort but also impaired mental vitality, may persist in patients for many weeks after an attack of influenza. The author observed in 4 patients with influenza a similar pattern of symptoms, consisting of fatigue, muscular weakness, severe dyspnea, aching limbs, and mental depression associated with low blood pressure. These symptoms suggested adrenocortical insufficiency. Determination of serum electrolyte and urinary steroid excretion levels supported this view, but correction of hyponatremia and increased urinary steroid excretion after corticotropin administration indicated that adrenocortical insufficiency was secondary to reduced anterior-pituitary activity. Rapid improvement occurred in each patient during administration of corticotropin and later of prednisolone. In 1 patient severe mental depression and electroencephalographic abnormalities disappeared after steroid therapy.

Factors Influencing the Course and Prognosis of Systemic Lupus Erythematosus. R. P. McCombs and J. F. Patterson. New England J. Med. **260**:1195-1204 (June 11) 1959 [Boston].

By analyzing the clinical data in 77 patients with systemic lupus erythematosus seen at the New England Center Hospital, Boston, the authors evaluated the prognostic implications of sex, age, manifestations of the disease, pregnancy complicating the disease, and corticosteroid therapy. While the disease occurred much less frequently in men, it was more severe and carried a much higher mortality than in women. When the diagnosis was established before the age of 21 years the prognosis was grave, but when the diagnosis was established after the age of 45 years it was favorable.

Evidence of renal involvement, even when the abnormalities of the urine were mild at first, was the most serious prognostic omen. Corticosteroid therapy did not prevent the progression of established renal disease, but it seemed to have some effect in preventing it, and certainly it did not induce it. Polyserositis and myocarditis, when not associated with renal failure, responded to corticosteroid therapy, and consequently prognosis in this group was favorable. Encephalitis, similarly, when not associated with renal disease, responded to corticosteroid therapy. Hemolytic anemia and thrombocytopenic purpura were occasional early manifestations of systemic lupus erythematosus but, in a small group, most patients who had these disorders later had serious features, from which many of them died. Pregnancy seemed to be a precipitating factor in the onset of some cases of systemic lupus erythematosus. However, once the disease was established, and in the absence of renal disease, pregnancy was safely undertaken with reasonable expectation of delivery of normal babies.

Corticosteroid therapy had a suppressive effect upon the rash, fever, pleurisy, pericarditis, peritonitis, pneumonitis, and hematological and neurological complications of systemic lupus erythematosus. It had little effect upon the renal lesions of the disease. Untreated patients usually died in the acute, "toxic" phase of the disease, whereas adequately treated patients had a much lower mortality. Deaths in treated cases were due to renal failure or complications of corticosteroid therapy.

The Management of Idiopathic Thrombocytopenic Purpura. A. A. Cooperberg. Canad. M. A. J. **80**:937-943 (June 15) 1959 [Toronto].

Twenty-three consecutive patients with idiopathic thrombocytopenic purpura are reviewed in this paper. The disease is characterized by a hemorrhagic state associated with a reduction in the number of circulating blood platelets. Despite the low platelet count in the peripheral blood, the number of megakaryocytes in the bone marrow is normal or increased. Since Werlhof's first description of this disease, no effective therapy was available until 1916, when Kaznelson recommended splenectomy. There was no explanation for the success of splenectomy, and the operation is still performed on an empirical basis. All of the 23 patients had typical petechiae and other hemorrhagic phenomena, and platelet counts of less than 90,000 per cubic millimeter. Six were children under 6 years of age and 17 were adults over 19 years of age; 20 were females and 3 were males.

Cortisone, hydrocortisone, and prednisone were the corticosteroids used in the treatment of 14 of the 23 patients. The initial dose of cortisone was 200 mg. daily, of hydrocortisone 160 mg. daily, and of prednisone 40 mg. daily, in divided doses. The dosage was reduced as the platelet counts improved. Most patients were treated with prednisone. Three patients died of cerebral hemorrhage before corticosteroids were available. There were no deaths in those treated with corticosteroids. Of the 14 cases treated with steroids, 10 were acute and had a complete remission, whereas 4 were chronic with a temporary remission. Three of the patients with chronic purpura had a splenectomy which was followed by a complete remission.

It is concluded that all patients with thrombocytopenic purpura should be treated with large doses of corticosteroids as soon as the diagnosis is made. This applies to patients with thrombocytopenic purpura due to drug sensitivity and to symptomatic thrombocytopenic purpura as well. Hemorrhage is thus rapidly controlled and the platelet

count is increased to normal. In most cases, splenectomy may be avoided. When thrombocytopenia recurs as the corticosteroid dosage is reduced, splenectomy will ultimately be required. Preparation of a patient for splenectomy with corticosteroids has made this a safe and elective procedure, rather than the hazardous emergency operation of former years. Where relapse occurs after splenectomy, the corticosteroids may be used either continuously or intermittently, as indicated, to reduce the risk of serious hemorrhage. To minimize side-reactions, small doses of steroids may be sufficient to attain the desired effect without attempting to reach normal platelet levels.

Macroglobulinemia of Waldenström and Gastric Ulcer. R. Cattan, P. Vesin, J. L. Bonnet and M. Hivet. Presse méd. **67**:1068-1071 (May 27) 1959 (In French) [Paris].

Macroglobulinemia of Waldenström was demonstrated in a 63-year-old man admitted to the hospital because of 2 profuse hematemeses and subsequent melena complicating an ulcer of the lesser curvature of the stomach. The clinical, biological, and hematological aspects of the disease are described. The possible relation of macroglobulinemia of Waldenström to gastric ulcer, hepatic lesions, and the nosology of the disease was investigated, with particular attention to its connection with lymphoid leukemia, plasmocytic myeloma, and with certain forms of cirrhosis associated with hyperproteinemia.

Secondary Amyloidosis in Leprosy. Amyloidosis and Leprous Reaction. J. G. Masanti. Medicina **19**:1-10 (Feb.) 1959 (In Spanish) [Buenos Aires].

Three hundred six patients with leprosy in the Baldomero Sommer Leprosarium of Buenos Aires were observed. The disease was lepromatous in 263 patients and benign in 43. The incidence and causal factors of amyloidosis were investigated. A diagnosis of amyloidosis was made by the clinical symptoms and by the results of either or both the Cohen and Benhold tests. The presence of amyloidosis was proved in 4 out of 160 patients with quiescent lepromatous leprosy, in 15 patients out of 100 with the reactional type of lepromatous leprosy, and in 2 out of 43 patients with benign clinical forms of leprosy. In all the patients with the reactional type of lepromatous leprosy the reactional bouts started within the first year from the appearance of leprosy. The reactions were severe, febrile, and recurrent. They were followed by the appearance of albuminuria (showing amyloidosic involvement of the kidney) within a period which varied between 7 months and 3 years after starting of the leprous reactions. The author concludes that lepromatous leprosy of the nonreactional type and benign leprosy are complicated by amyloidosis only in rare cases (2.5% and 4.5% respectively). Amyloidosis is frequent in the reactional type of lepromatous leprosy (15%). The main causal factor of amyloidosis is the acute reaction in itself. Amyloidosis of reactional leprosy rapidly damages the kidney, causing renal insufficiency and final uremia in a period of 1 to 5 years.

A Fatal Case of "Q" Fever Associated with Hepatic Necrosis. J. I. Tonge and E. H. Derrick. M. J. Australia **1**:594-597 (May 2) 1959 [Sydney].

A meatworker, aged 52 years, had an acute attack of "Q" fever. Enlargement of the liver appeared on the 12th day, and jaundice on the 14th; death occurred on the 17th day. The patient's final illness was due, wholly or partly, to an acute infection with Coxiella burnetii. This diagnosis was established by the demonstration in mice of the characteristic Rickettsia organisms derived from the patient's urine, and by the development of specific agglutinins in his serum. Guinea pigs inoculated with urine and liver-kidney-spleen produced febrile reactions consistent with "Q" fever, and this effect was manifest in repeated passages. The lesions found at post mortem were widespread. The most prominent, and probably the most lethal, finding was the extensive, diffuse necrosis of the liver. Other findings were acute interstitial nephritis, interstitial pneumonia, bronchopneumonia, and encephalitis. The question whether the liver damage was due solely to C. burnetii or whether other factors contributed is difficult to answer on the evidence available. Hepatic involvement is often associated with an attack of "Q" fever, and the frequency of this association suggests a causal relation. It is also possible, however, that the patient had a simultaneous infection with the virus of infective hepatitis.

Studies of Erythrocyte Survival in Acute Leukemia. D. M. Whitelaw, K. A. Evelyn and P. F. Solvonuk. Canad. M. A. J. **80**:944-948 (June 15) 1959 [Toronto].

The introduction of radioactive chromium for tagging red blood cells and estimating blood volume and erythrocyte survival time provided a relatively simple technique for evaluation of the presence and degree of hemolysis. The authors used this method in 12 patients with blast cell leukemias, in 10 of whom the disease first manifested itself as acute leukemia, one patient had polycythemia vera culminating in acute leukemia, and another one had chronic granulocytic leukemia, with an acute terminal phase. Most of the subjects were tested shortly after the diagnosis was made, but 1 patient was tested 4 months and again 8 months after diagnosis. In the method used, approximately 15 ml. of the patient's venous blood was withdrawn by syringe and injected into a sterile, silicone-

treated, rubber-stoppered 100-ml. vial containing 5 ml. of acid citrate dextrose (ACD) solution and about 100 microcuries of Cr^{51} as $Na_2Cr^{51}O_4$ (radioactive sodium chromate). The mixture was allowed to stand at room temperature for 20 to 60 minutes, then 50 mg. of ascorbic acid was added in order to reduce the chromium remaining in the plasma to the trivalent form and thus prevent further uptake of chromium by the red blood cells. After thorough mixing, 10 ml. of chromated blood was drawn into a calibrated syringe and injected into the patient through the rubber tubing of a freely running intravenous infusion set. The remaining blood was used to determine the hematocrit value and to prepare samples of whole blood and plasma for radioactive counting at a later date.

It was found that the radioactive chromium method for studying red blood cell survival is applicable to short-term observations in acute leukemia where more prolonged studies would be impractical because of the necessities of treatment, including blood transfusions. It is essential that the red blood cell volume be measured at the beginning and at the end of the studies in order to correct the survival curve for alterations in red blood cell volume occurring during the experiment. About two-thirds of the patients studied showed a moderate or marked reduction in red blood cell survival. The curves showed a satisfactory degree of internal consistency and, where prolonged to 10 or 14 days, showed no tendency to deviate importantly from the early trend. While minor degrees of hemolysis might escape detection because of so brief a period of observation, it is evident that the method is sensitive enough to show hemolysis not brought out by other laboratory procedures. No correlation was apparent between the results of the survival studies and those of other laboratory tests used to indicate hemolysis. The rate of fall of hemoglobin value was closely related to the red blood cell survival.

Cryptococcosis: Further Observations and Experience with Amphotericin B. W. J. Martin, D. R. Nichols, H. J. Svien and J. A. Ulrich. A. M. A. Arch. Int. Med. **104**:4-14 (July) 1959 [Chicago].

The authors studied 8 patients with cryptococcosis; the cases of 5 of these patients who had meningoencephalitis due to an infection by Cryptococcus neoformans, which was associated in 1 patient with Hodgkin's disease, are described. Cultures of the spinal fluid were positive for cryptococcosis in all 5 patients. Amphotericin B was administered by the intravenous route in 4 patients and by the intravenous, intrathecal, and intraventricular routes in the patient with Hodgkin's disease. The authors recommend that, when amphotericin B is given intravenously, each milligram of the agent should be dissolved in at least 5 ml. of 5% dextrose in distilled water. Treatment was started with an initial dose of 0.25 mg. of amphotericin B per kilogram of body weight, administered intravenously in 6 to 12 hours. The dose was gradually increased to approximately 1 mg. per kilogram of body weight, depending on the tolerance of the patient. Side-effects, such as phlebitis at the site of injection, headaches, flushing, chills, fever, dyspepsia, and azotemia, occurred; but these symptoms subsided when injections were administered at longer intervals, when the daily dosage was decreased, or when treatment was temporarily interrupted. The drug had no toxic effect on the hematopoietic system or on the liver function, and there was no evidence of irreversible damage to the kidneys.

The daily doses of amphotericin B, ranging from 50 to 100 mg. and administered for approximately 6 weeks, seemed to have arrested cryptococcic meningoencephalitis in 3 patients in whom the spinal fluid became free of fungi on repeated cultures. One patient was a treatment failure. Relapses occurred in 2 patients, one of whom had Hodgkin's disease, but even in the latter patient the drug afforded several months of continued existence. Final judgment as to the effectiveness of amphotericin B cannot be made, since the follow-up in these patients after termination of therapy has not been sufficiently long; however, it appears to be a promising anticryptococcic agent, even when the natural tendency of the disease to spontaneous remission of prolonged duration is taken into consideration.

The Syndrome of Acute Disseminated Moniliasis in Adults. A. I. Braude and J. A. Rock. A. M. A. Arch. Int. Med. **104**:91-100 (July) 1959 [Chicago].

An attempt was made to define the clinical syndrome of systemic moniliasis and to determine the disturbance in resistance responsible for such infections in adults. The authors report a 55-year-old man with acute disseminated moniliasis and review 4 cases of this disease cited in the literature. The study has been limited to fatal cases of generalized moniliasis, in which the etiology was definitely established by isolation and identification of Candida albicans, and does not include localized infections of the meninges, lungs, or endocardium. There are 2 striking clinical features of this infection: (1) a background of continuous antibiotic treatment during a protracted debilitating illness, and (2) an abrupt decline in the clinical course with the development of fever, shock, mental depression, leukocytosis, and gastrointestinal hemorrhages. In 3 patients death occurred within 5 days after cultures revealed C. albicans. All the patients had been treated with one of the tetracyclines, and 3 had also received streptomycin and chloramphenicol. These antibiotics were given in large doses for periods ranging from 11 to 31

days before C. albicans was recovered by blood culture. Pancreatitis was the cause of admission in 2 of the patients, and neurological disease in another 2. The main findings at autopsy were mycotic abscesses of the kidney, heart, and brain. In 2 patients these abscesses were also found in the pancreas, and in 1 patient in the adrenal and the liver.

Culturally proved cases of the disease have been rarely recognized in adults, and no reports could be found in the literature before the advent of antibiotics. It is possible, therefore, that antibiotics play a decisive part in lowering the resistance of adults to C. albicans by suppressing the normal bacterial flora. Hypocalcemia, also a finding in the authors' patient, may have a possible significance in lowering host resistance to C. albicans. Nystatin has been effective in eliminating Candida organisms from the intestine and has an important place in prophylactic treatment of debilitated patients who are predisposed to moniliasis through prolonged antibiotic therapy.

Influence of Myocardial Infarction on Plasma-Lipoprotein Concentration. C. Dodds and G. L. Mills. Lancet 1:1160-1163 (June 6) 1959 [London].

Three methods of analysis—ultracentrifugation, Cohn fractionation, and paper electrophoresis—were used to study the lipoprotein patterns of the blood in a group of 220 healthy male volunteers, of an average age of 56 years, who had no clinical symptoms of coronary artery disease. The same 3 methods were used also in 2 groups of patients with coronary artery disease. The first group (group 1 infarcts) included 19 men who had suffered a myocardial infarct about 6 weeks earlier and from whom only one specimen was obtained. The second group (group 2 infarcts) comprised patients under treatment in hospital for myocardial infarction from whom samples were taken, where possible, within 24 hours of the attack, 3 or 4 days later, and thereafter at intervals of 7 days; this group included 78 patients of an average age of 58 years.

The measurements revealed that a myocardial infarction is itself associated with a pronounced lipoprotein abnormality which is manifest for at least 2 months after the attack. The condition of the lipoprotein pattern during this period cannot be summarized by a single measurement, and it is therefore inadmissible to compare analyses of this kind with those of a group of healthy men. The only certain way of separating the lipoprotein abnormalities due to an infarction from those which may precede it is to examine the blood of men both before and after an attack. The results obtained support the observation by others that the relatively acute atherogenic disease leading to myocardial infarction in young men (under 45) is preceded and accompanied by more pronounced lipoprotein abnormalities than the slowly developing coronary-artery disease of the elderly. In the latter, the lipoprotein patterns are more often "normal."

It may be concluded that the lipoproteins of the blood are, in certain cases, concerned with the development of coronary-artery disease and also that the effect of the infarct itself on the lipoprotein pattern has, in many cases mistakenly, been ignored. As a result, some investigators have used lipoprotein analyses with unwarranted confidence and freedom, while others have been undeservedly skeptical about them.

Acquired Hemolytic Anemia in Chronic Lymphocytic Leukemia and the Lymphomas: Survival and Response to Therapy in Twenty-Seven Cases. R. A. Kyle, J. M. Kiely and J. M. Stickney. A. M. A. Arch. Int. Med. **104**:61-67 (July) 1959 [Chicago].

The records of 27 patients with hemolytic anemia associated with malignant disease, who were hospitalized at the Mayo Clinic between 1945 and 1957, are reviewed. Severe anemia was associated with chronic lymphocytic leukemia in 16 patients, with Hodgkin's disease in 7, with follicular lymphoma in 3, and with lymphosarcoma in 1. Hemolytic anemia was responsible for the initial symptoms and led to the diagnosis of the underlying disease in the majority of the patients with lymphoma, whereas in most of the patients with leukemia the diagnosis of anemia was made later. All the patients received standard treatment for their underlying malignant lymphocytic disease, including irradiation therapy, the administration of mechlorethamine hydrochloride and triethylene melamine, and blood transfusions. An attempt was made to evaluate the effect of adrenocortical steroids and corticotropin (ACTH) on anemia during 28 hemolytic episodes in 16 patients. The results of this therapy were exellent in 9 instances, fair in 15, and poor in 4. One patient who had received little benefit from cortisone responded dramatically to the intravenous administration of corticotropin. Also, another patient obtained complete remission by use of corticotropin, whereas he had had only temporary remission with cortisone therapy. There were only a few serious side-effects from adrenocortical medication because of the short duration of therapy in most patients. The response to cortisone and corticotropin therapy was not related to the type of underlying malignant lymphocytic disease. The effect of various standard treatments on the hemolytic process could not be individually evaluated.

The follow-up showed that among the 27 patients 8 were alive at the time of this report; 6 of these have had no particular trouble, either from the malignant lymphocytic disease or from the hemolytic process, and mild hemolysis has continued in 2. Eighteen patients died. The deaths of

8 were due to a combination of hemolysis and the malignant disease; 4 had no hemolysis at the time of death; no details about the deaths of the other 6 are known. One patient was lost for follow-up. It is important to recognize the presence of hemolytic anemia in patients with chronic lymphocytic leukemia or with malignant lymphoma in order to institute proper therapy. Although treatment with adrenocortical steroids and corticotropin has little to offer patients with chronic lymphocytic leukemia or with malignant lymphoma without the association of hemolytic anemia, these drugs often bring about remarkable improvement in patients with this complication.

Treatment of the Angina Syndrome: Results of the Use of Iproniazid. J. A. Barrera and R. G. Turiella. Prensa méd. argent. **47**:111-115 (Jan. 9) 1959 (In Spanish) [Buenos Aires].

Fifty outpatients who had been given a diagnosis of angina pectoris (established by history and electrocardiographic evidence of ischemia, cardiac lesions, or myocardial infarction) were treated with iproniazid. There were 33 men and 17 women in the series, their ages ranging from 30 to 80 years. The patients received an initial dose of iproniazid of a lower level than usual, i. e., 75 mg. daily, divided into 3 doses of 25 mg. Only in the severer cases was the daily dose increased to 150 mg. The average duration of treatment was approximately 68 days. Each patient reported for examination once a week. The results of this therapy varied from complete relief from the symptoms of angina pectoris to no relief. According to the degree of relief reported, the patients were divided into 5 groups. The improvement obtained was estimated as 100% in group 1 (17 patients or 34% of the total series); 75% in group 2 (8 patients or 16% of the total number); 50% in group 3 (14 patients or 28% of the series); 25% in group 4 (5 patients or 10% of the series); and 0 in group 5 (6 patients or 12% of the series). The beneficial effects of iproniazid were manifest within one week to one month of the therapy. In some patients the improvement persisted even after discontinuation of the treatment; in others the symptoms reappeared on omission of the drug and again disappeared when the treatment was reinstituted. Thirty-two patients suffered side-effects of varied kinds and degrees. Six of them experienced sexual impotence, which in one persisted even after the administration of iproniazid had been suspended. The intensity of the undesirable effects led to the interruption of the treatment in 15 patients; in 5 of these it could be reinstated.

It is the authors' impression that the administration of iproniazid is the first effective therapy encountered in treating the angina syndrome. They point out the danger of untoward effects, however, and recommend the use of smaller doses than usual, especially at the start. The initial dose should be 75 mg. or less, and the patients should be closely watched during the entire treatment.

Prednisone Given Alone and in Combination with Chloramphenicol in the Treatment of Typhoid: Clinical, Bacteriological, and Serologic Observations in 100 Cases. C. F. Colucci. Presse méd. **67**: 725-728 (April 11) 1959 (In French) [Paris].

Clinical studies have been carried out to evaluate the effect of synthetic glucocorticoids, given alone or in conjunction with chloramphenicol, in a total of 100 patients with mild typhoid. All the patients presented practically identical initial agglutinin levels; the duration of their disease ranged from 10 to 20 days, and no treatment had previously been given them other than symptomatic therapy. The patients were divided into 3 groups. The first group consisted of 36 patients who were given prednisone orally, or prednisolone by injections, for periods ranging from 10 to 18 days, in total doses varying from 550 to 870 mg., depending on body weight. The second group of 34 patients received prednisone orally, or prednisolone parenterally, for a period of 12 days, with total doses of 215 to 310 mg., depending on body weight; these patients were also simultaneously given small doses of chloramphenicol for 14 days, the total dose varying from 14 to 18 Gm., depending on body weight. The third group consisted of 30 patients who served as controls and who were given small doses of chloramphenicol alone for 18 days, with total doses ranging from 18 to 23 Gm., depending on body weight. Symptomatic treatment was also given to all the patients.

Comparison of the results obtained in the 3 groups showed that cortisone and the synthetic glucocorticoids are well tolerated even if administered for a prolonged time, but that their therapeutic action is limited when given alone. These drugs have proved to be significantly inferior to chloramphenicol. The best results were obtained in the second group with the administration of chloramphenicol in conjunction with prednisone or prednisolone, which brought about a rapid cure, without recurrence, in 50% of the patients. The results obtained with chloramphenicol in association with prednisone or prednisolone were far superior to those obtained with either these hormones or chloramphenicol alone.

The author advocates administering synthetic glucocorticoids in association with chloramphenicol in small doses for fairly long periods, with total doses ranging from 215 to 310 mg. for glucocorticoids, and from 14 to 18 Gm. for chloramphenicol. This regimen produces, in addition to a reduction of the excessive organic reaction, a gradual bacteriostasis with the help of the immunizing powers of

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the body. Thus, the damage that may be caused by bacteriolysis can be avoided, because, on the one hand, this is produced gradually, and, on the other, the body is protected against it by the prolonged hormone therapy.

Factor-VII Deficiency with Christmas Disease in One Family. F. Nour-Eldin and J. F. Wilkinson. Lancet 1:1173-1176 (June 6) 1959 [London].

The incidence of Christmas disease or plasma thromboplastin component deficiency is estimated at about 2 per million of the population in England and Wales. Congenital deficiency of factor VII seems to be even rarer. The authors present 2 related patients (a 21-year-old man and his 76-year-old maternal grandfather) whose clinical picture and family history suggested a hemophilia-like disease. Routine blood-clotting tests showed, in both cases, a combined deficiency of factor VII and Christmas factor. A study on the effect of the plasma of these patients on the stage of plasma thromboplastin formation demonstrated the presence of Bridge anticoagulant, thus proving the presence of true Christmas disease. It is shown that the conjoint anomaly was inherited as a sex-linked recessive character.

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Coarctation of the Aorta Followed for Twenty-Five Years. H. Cookson. Lancet 1:1178-1180 (June 6) 1959 [London].

A diagnosis of coarctation of the aorta was made in 1933 in a 38-year-old woman. She had angina of effort, anxiety symptoms, and a toxic goiter which was treated by total thyroidectomy in 1935; this operation had a good effect on all the symptoms. After 1936 she was not seen for 6 years when she reported that over this period she had been "wonderful" and had been able to do her own housework, but she now had pain in the region of the left breast and in the left arm, throbbing in the neck and ears, some falling-out of her hair, and a feeling of cold. Moreover, the skin was dry and coarse, and there was slight cardiac enlargement, coarse duplication of the apical first sound, and a late-systolic murmur. There was further gradual deterioration during the next 15 years; the electrocardiogram of 1933 and the one taken on the day of death in 1958 were very similar, although transient ischemic T-wave changes had been recorded in the intervening period. During this time the brachial blood pressure showed some variations, but there was little change in the mean pressure throughout the course, the systolic reading falling and, to a less extent, the diastolic reading rising. In spite of the burden of hypertension, which was probably life long, and the severe and extensive coronary obstruction, heart failure of an incapacitating degree did not occur until 4 days before death. The almost exact similarity of the final electrocardiogram to the one taken 25 years previously, despite the finding of extreme coronary narrowing, is to be explained by the equal distribution of the ischemia throughout the myocardium, with no local area of acute necrosis.

The review of Reifenstein and associates in 1947 put congestive heart failure as the third commonest cause of death in patients with coarctation, excluding incidental causes, which head the list. Rupture of the aorta and bacterial endocarditis or aortitis were found to cause death more frequently than congestive failure. In the case reported by the author, massive calcification of the aorta proximal to the coarctation may have protected it from rupture, while the normal aortic cusps would lessen the liability to endocarditis.

Edematous Malignant Exophthalmos Revealing a Leukosis: Pathogenetic Discussion. H. Giroire, A. Charbonnel, J.-P. Kernéis and P. Lemouroux. Presse méd. 67:817-820 (April 22) 1959 (In French) [Paris].

The authors present the case of an 18-year-old youth with malignant edematous exophthalmos that was the first sign of a leukosis. On admission to the hospital, the patient said that the exophthalmos had appeared suddenly while he was in good health 2 months before the observation. Weakness, pallor, and some loss of weight were noticed at this time. Ophthalmological examination revealed that the exophthalmos, measured with Hertel's exophthalmometer, amounted to 26 mm. in each eye. Visual acuity was perfect, the fundus oculi was normal, and the field of vision was complete. Basal metabolism was increased slightly, but the iodine fixation test gave normal results. The blood test, which was the key to the etiological problem, showed a red blood cell count of 2,650,000 per cubic millimeter and a white blood cell count of 18,400, while the percentage of leukoblasts was 95%. The patient was given Cortancyl with transfusions, and later Purinethol and antibiotics; then he had 5 sessions of radiotherapy to the retro-orbital region. Thereafter the general condition of the patient improved, the body weight increased, the red blood cell count increased to 5.5 million per cubic millimeter, while the white blood cell count dropped to 11,000, and the leukoblast percentage to 90%. The condition of the eyes improved greatly: the edematous infiltration of the eyelids became less marked, the exophthalmos was reduced to 23 mm. in each eye, and complete closure of both eyes again became possible. The retinal vessels became more accentuated, and the retina looked striated, especially in the interpapillary ocular region. A mild edematous infiltration near the temporal segment of the papilla, with no hemorrhage or exudate, was noticed on the left side, however. This aspect of the fundus oculi revealed the incipient edematous infiltration of the retina.

Sometime later the patient returned to the hospital with severe stomatitis, greatly enlarged cervical lymph nodes on the left side, and fever. The red blood cell count had decreased to 2 million per cubic millimeter, while the white blood cell count had increased to 29,000, and the percentage of leukoblasts to 100%. The condition of the patient became increasingly worse. Rapidly generalized purpura set in, followed by profuse visceral hemorrhage, progressive coma, and death. On autopsy, the pituitary origin of the exophthalmos was confirmed. The authors point out that the hypophysis may secrete an exophthalmos-inducing hormone differing from the so-called thyrotropic hormone and that leukosis should, therefore, be considered as one of the conditions that may cause edematous malignant exophthalmos by way of a hypophysial infiltrate.

Aludrine Test and Peripheral Leukocytes. F. F. C. Moreno. Rev. clin. espaň. **72**:151-155 (Feb. 15) 1959 (In Spanish) [Madrid].

When establishing the diagnosis of a pulmonary condition, it is of great importance to determine whether the cause is a functional reversible process or an organic irreversible change. The Aludrine test is recommended by the author as adequate for this purpose. Eighteen patients, taken at random as they applied for consultation, were given the Aludrine test after a preliminary determination of total pulmonary capacity, quantity of air expired, velocity of expiration, and leukocytic formula. Aludrine was administered in a 1/1,000 solution and inhaled in 12 deep inspirations. The test was considered positive when on repetition of the determinations made before the inhalation of Aludrine there was an increase in the respiratory output, especially in the velocity of the expiration and in the volume of air expired during the first second after a deep inspiration.

Of the 18 patients studied, 11 showed positive results and 7 negative results. In the group with a positive test, 8 patients showed also an increase in the number of peripheral leukocytes, 1 showed negligible increase or decrease, and 2 showed a definite decrease. In the negative test group, there was only one patient with a definite increase in peripheral leukocytes, while 5 had negligible variations and one had a definite decrease. A comparison of the leukocytic formulas, taken before and after the test, indicated that variations in the number of leukocytes were produced mainly at the expense of the granulocytes, especially of the eosinophils. The author concludes that the implication of a positive Aludrine test is the existence of a reversible bronchial spasm, which is improved by medication, and that the accompanying leukocytosis constitutes the response to another pulmonary function, i. e., the regulation of peripheral leukocytes.

Treatment of Crohn's Disease with Deltacortisone. R. Crismer and C. Drèze. Acta gastro-enterol. belg. **22**:229-243 (April) 1959 (In French) [Brussels].

Deltacortisone (or prednisone) was used in the treatment of 8 patients with Crohn's disease (distal, regional, or terminal ileitis). The first 2 patients showed a temporary improvement, not, perhaps, entirely due to the drug, which lasted for 3 months. Deltacortisone, however, did not prevent the development of intraparietal fistulas in these 2 patients or the extension of the disease process in one of them. It should be noted that in each case the disease had reached a stage in which fibrosis secondary to edematous reaction was such that deltacortisone was incapable of preventing the complications of lymphatic blockage. The results, in general, seem to show that deltacortisone is effective in the treatment of Crohn's disease when it is still in the follicular stage of ileitis, either primary or recurring after operation. The disappearance of pain and diarrhea in such cases is usually accompanied by the restoration of anatomic and radiologic integrity.

The benefit derived from deltacortisone seems to be due, on the one hand, to its effect on the general condition and, on the other, to its anti-inflammatory and antifibroblastic effect. Its action is probably potentiated by the concomitant administration of antibiotics. The authors prescribed deltacortisone in a daily dose of 20 mg., sometimes for several months, combined with sulfaguanidine (8 Gm.) and chloramphenicol (2 Gm.) to prevent the infectious complications sometimes associated with the use of deltacortisone, and to assure good intestinal sterilization. Deltacortisone was well tolerated by all the patients, although glossitis appeared in one in whom a laryngeal smear revealed the presence of Candida albicans.

SURGERY

Considerations of the Rationale and Technique of Coronary Endarterectomy for Angina Pectoris. J. A. Cannon, W. P. Longmire Jr. and A. A. Kattus. Surgery **46**:197-211 (July) 1959 [St. Louis].

In the course of experience with the direct surgery of obliterative atherosclerosis of the terminal aorta and its distal branches, it occurred to the authors that the pathological manifestations in the coronary arteries are comparable to those found in the femoropopliteal region of the arterial tree. Obliterative atherosclerosis is a disease of relatively large vessels. Its obstructive component tends to be maximum in the region of arterial bifurcations. The primary disease is the subintimal collection of lipoprotein which results in narrowing and eventual occlusion of the lumen. Thrombus formation is encountered only as a secondary

phenomenon. In the treatment of femoropopliteal obliterative disease, one of the authors developed a semiclosed technique of endarterectomy, based upon the fact that a definite cleavage plane exists in atherosclerosis between a relatively intact outer arterial wall consisting of media and adventitia and the thickened subintimal plaque. It is also to be noted that the occlusions are segmental, and the arterial tree distal to an occlusion tends to remain patent. The continued patency of this distal tree is the essential requirement for successful direct arterial surgery.

After using the semiclosed thromboendarterectomy successfully in the treatment of the popliteal and posterior tibial arteries, it occurred to the authors that the same technique with suitable modification might be applicable to obliterative coronary atherosclerosis. Since that time a research program has been under way to study the possibility. Investigation of this problem has been pursued along 4 main avenues: (1) pathological study of coronary atherosclerosis in terms of feasibility of direct surgical attack; (2) elaboration of a surgical technique; (3) determination of criteria for candidate selection; and (4) clinical experience. Pathological findings justify coronary endarterectomy in severe angina pectoris due to obliterative coronary atherosclerosis. The feasibility of reestablishment of blood flow through a formerly obstructed coronary arterial segment has been proved by animal experimentation. An objective method permitting diagnosis, case selection, and postoperative objective evaluation of results has been elaborated. The authors show in illustrations the special instruments used and also the basic steps in the technique of coronary endarterectomy by intraluminal stripping under direct vision.

Nine patients with severe intractable angina pectoris were subjected to coronary endarterectomy. Five survived the operation, and all have shown improvement as measured by subjective and objective clinical evaluation and as confirmed by postoperative treadmill exercise electrocardiograms. The greatest problem in accomplishing the operation did not so much concern the dissection on or in the arteries, or problems of removing the proximal or distal core, or problems in closure of an arteriotomy. Rather, it concerned the intermittent myocardial sluggishness and irritability especially of the left ventricle.

Thyroid Cancer and Its Treatment. J. W. Welch, C. A. Hellwig, V. E. Chesky and E. N. McCusker. Surg. Gynec. & Obst. **109**:27-37 (July) 1959 [Chicago].

At the Hertzler Clinic, Halstead, Kan., 3,024 patients were operated on for thyroid disease in the 15-year period from 1940 to 1956. Pathological studies confirmed the presence of thyroid cancer in 267 (or 8.8%) of these. The authors divide the thyroid carcinomas into 2 groups, a favorable and an unfavorable one. The favorable group includes pure papilloma, papilloma with follicular variant, follicular carcinoma, Hürthle cell carcinoma, invasive adenoma, and clear cell carcinoma. In this favorable group the over-all survival rate was 80%. The unfavorable group includes giant cell carcinoma, small round cell carcinoma, malignant lymphoma, hemangio-endothelioma, and diffuse carcinoma. In this unfavorable group the over-all survival rate was 35%.

The authors believe that conservative surgery alone, consisting largely of lobectomy and bilateral subtotal thyroidectomy, is adequate therapy for the less malignant forms of thyroid cancer. In the more malignant forms therapy should consist of total thyroidectomy, with a modified neck dissection and postoperative adjuvant therapy. The authors agree with Crile as regards the fallacy of the radical en bloc dissection for thyroid cancer. They show that excision of all involved lymph drainage and involved contiguous structures cleanly and en bloc is incompatible with life. A modified neck dissection (excision of all involved nodes which can be dissected free) is more pragmatic. This type of surgery may then be followed by hormone therapy, in the form of desiccated thyroid extract.

Surgical Treatment of Achalasia of the Esophagus. C. Edward, B. Abbot, W. C. MacKenzie and C. A. Ross. Canad. J. Surg. **2**:345-352 (July) 1959 [Toronto].

Twenty-five patients with achalasia of the esophagus, who have been operated on, form the basis of this review. Twenty-two patients were treated by a modified Heller operation, while 3 had various reconstructive procedures on the gastroesophageal junction. Heller used an esophagogastric extramucosal myotomy anteriorly and posteriorly. The abdominal approach is favored by most surgeons for patients with achalasia of the esophagus. In the 22 patients undergoing the modified operation, the authors used the abdominal approach 12 times and the thoracic approach 10 times. With the abdominal approach for the modified Heller operation, a midline incision is used, and the left lobe of the liver is mobilized well to the right by dividing the left triangular hepatic ligament. The peritoneum over the esophagogastric junction is divided transversely and the esophagus mobilized from its bed by blunt dissection with a finger. The left vagus nerve is identified and retracted to the right. The incision should extend far enough distally to be sure that all esophageal fibers are divided, and it should be kept to the right of the midline. The length of this incision will average 8-12 cm., and the mucous membrane should bulge freely into view. When the procedure is complete,

there should be no evidence that any circular bands of muscle fibers are constricting the mucosa. No attempt is made to approximate the peritoneum over the defect in the muscle wall.

Seventeen of the 22 patients in whom the modified Heller operation has been used obtained excellent results with no recurrence of dysphagia and no clinical evidence of regurgitation or esophagitis. Two patients have been classified as having had a good result, although an occasional bout of dysphagia has been experienced, especially when eating too rapidly. In 3 patients a poor result was obtained; however, review of the records revealed that insufficient indications were present to warrant the operative procedure. All 25 patients have been assessed, and no case has been lost to follow-up. Two patients have died of causes other than achalasia of the esophagus. In the group treated by a modified Heller procedure, the follow-up period averaged 3 years and 2 months. In the small group treated by gastroesophageal reconstruction, the time since operation has averaged 11 years. The authors conclude that a modified Heller esophagocardiomyotomy is the treatment of choice in achalasia of the esophagus.

Metabolic and Physiologic Observations on Patients Undergoing Extracorporeal Circulation in Conjunction with Hypothermia. W. G. Young Jr., W. C. Sealy, I. W. Brown Jr. and others. Surgery **46**:175-184 (July) 1959 [St. Louis].

Since January, 1956, intracardiac surgery has been performed on 111 patients at the Duke University Medical Center in Durham, N. C., utilizing a combination of extracorporeal circulation at moderately low flow rates and hypothermia. The authors present an analysis of the metabolic and physiological changes occurring in these patients during and after perfusion at an esophageal temperature of 28 to 32 C (82.4 to 89.6 F). For details of the extracorporeal circuit including heat exchanger, DeWall-type bubble oxygenator, and Sigmamotor pump, the authors refer to an earlier report. The induction and control of hypothermia were greatly improved by the incorporation of an efficient blood heat exchanger in the last 73 of the 111 patients.

It was found that at flow rates averaging 54 ml. per kilogram per minute for individuals under 35 kg. (78 lb.) in weight, and 31 ml. per kilogram per minute for heavier individuals, venous oxygen saturation can be maintained within the normal range if the esophageal temperature is reduced to 28 to 32 C (82.4 to 89.6 F). At this flow rate and temperature, metabolic acidosis is not encountered to a degree greater than that seen accompanying any major surgical procedure. Postoperative metabolic acidosis does not occur if myocardial efficiency is adequate. Oxygen consumption in patients perfused at 28 to 32 C was found to approximate one-half of that occurring at 37 C (98.6 F). Successful correction of severe tetralogy of Fallot in a patient whose esophageal temperature was reduced to 9.3 C (49 F) is described. Profound hypothermia permitted the use of very low flow rates, allowed temporary cessation of perfusion, and obviated the need for cardioplegic agents.

Implantation of Yttrium 90 into the Pituitary Body of Five Patients with Acromegaly. A. M. Dogliotti, A. Ruffo and G. M. Molinatti. Minerva med. **50**:1575-1578 (May 23) 1959 (In Italian) [Turin, Italy].

This study concerns 5 patients with acromegaly, who were treated by implantation of 5 small rods of radioyttrium (Y^{90}) through the nostril into the pituitary body. Three patients were followed up for a period of over a year, and 2 for 4½ months and 45 days, respectively, after the operation. The therapy produced subsidence of headache, sweating, excessive thirst, and backache; improvement in asthenia and polyphagia; and diminution in swelling of the extremities, tongue, and face. Less benefit was obtained for disorders of sexual function, except that libido was restored in one patient. Amelioration of the subjective symptoms was marked during the first month of therapy, but was less intense afterwards.

Phosphatemia, which had been present in one patient, was restored to normal values 22 months after the operation. Normalization of carbohydrate metabolism was obtained in 2 patients. A decrease of basal glycemia and of daily glycosuria was observed in one patient 13 months after the implantation. A slight disorder of carbohydrate metabolism, which was present in one patient before the implantation, deteriorated 45 days after the operation. This condition, however, may improve and may eventually disappear, because a similar change took place in 2 other patients whose carbohydrate metabolism normalized after the third postoperative month. Calcium metabolism was restored to normal 3 months after implantation in those patients who had a negative calcium tolerance test before the operation. Intense polyuria, which had developed immediately after the implantation, subsided within 15 to 20 days. No diminished function of the thyroid, adrenals, and gonads was observed.

PEDIATRICS

Intrahepatic Biliary Atresia. L. J. Krovetz. Journal-Lancet **79**:228-235 (June) 1959 [Minneapolis].

Detailed histories are given of 2 patients with intrahepatic biliary atresia, who were seen in recent years at the University of Minnesota Hospitals in Minneapolis. One of these patients is still alive at 16 years of age and is in good health except for

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severe generalized pruritus. This represents the longest period of survival of a patient with this condition that has been reported to date. The literature on both extrahepatic and intrahepatic biliary atresia is briefly reviewed. Only 23 cases of intrahepatic biliary atresia have been reported. Nine of these patients have survived more than 3 years, 6 of them being still alive when reported. The median age of survival of infants with extrahepatic biliary atresia which has not been relieved by surgery is only 4 to 6 months.

Dermatomyositis in Childhood: Report of Studies on 7 Cases and a Review of Literature. J. W. Carlisle and R. A. Good. Journal-Lancet 79:266-273 (June) 1959 [Minneapolis].

The histories of, and observations on, 7 children (4 girls and 3 boys) with dermatomyositis, who were studied at the University of Minnesota Hospitals, Minneapolis, since 1954, are presented. Age at onset ranged from 6 months to 13 years. Family histories failed to reveal other members with dermatomyositis, scleroderma, or acute lupus erythematosus. Insidious onset was characteristic. However, within weeks, the entire spectrum of skin manifestations, with the classical eyelid and butterfly heliotrope rash and extensor surface erythema, was evident. Periorbital edema was observed in all cases. Edema of ankles and hands was frequently present. Two children showed the chronic skin changes, described as poikiloderma, and consisting of atrophy and increased pigmentation of the skin. Calcinosis was observed by roentgenologic examination and biopsy in 3 cases. Palatorespiratory involvement with severe intercostal muscle weakness and late cardiac failure developed in one child, and death ensued. Fever was not a prominent feature in this series. Several children showed exacerbation following mild respiratory infection. In one child, the rash became more severe after exposure to sunlight. Dermatomyositis could not be related to bacterial or viral infections. Electrophoretic patterns were obtained on 6 of the children. Elevation of the alpha-2 globulin and gamma globulin components was regularly revealed. Examination of skin and muscle biopsy specimens by light microscopy demonstrated nonspecific myositis. The diagnosis must depend on the clinical manifestations.

The question of therapy remains unsettled. Three of the 7 children treated with steroids showed continued progression of weakness, pain, fever, and rash throughout steroid therapy. On the other hand, 4 children had a less severe course during moderate steroid therapy. However, 3 of these children showed calcinosis by x-ray examination. With the exception of specific change on biopsy or improvement on specific muscle testing, it is most difficult to relate prognosis to steroid therapy. The absence of dramatic improvement in response to steroid therapy and the high incidence of gastric or duodenal ulcers (3 of 6 children) raise the question of whether or not steroid hormones should be used in these patients.

Pulmonary Congestion and Edema as a Complication of Acute Nephritis in Childhood. R. A. Toro-Nazario and E. C. Burke. Journal-Lancet 79:246-253 (June) 1959 [Minneapolis].

Pulmonary edema is an uncommon, though serious, complication of glomerulonephritis in children. Because the authors could not find a report of the incidence of this complication in pediatric patients with nephritis, they examined the records of all children with acute or chronic glomerulonephritis seen at the Mayo Clinic in the years 1950-1957 to ascertain the frequency and clinical course of this complication. In this 8-year period, 89 cases of acute nephritis and 4 cases of chronic nephritis were encountered. A table listing the various complications of nephritis in these 93 children shows that 5 had pulmonary edema. After reviewing the literature on the subject, the authors discuss the clinical aspects, pointing out that pulmonary congestion and edema as a complication of nephritis can be acute and fulminating, with all the signs and symptoms of cardiorespiratory embarrassment, or it can be insidious, producing few, if any, clinical findings. Pulmonary edema may be transient and may subside rapidly as the general condition of the patient improves, or it may lead rapidly to death. The fact that the edema can be subacute, with few clinical findings, may explain, in part, why this condition is so rarely recognized.

Roentgenographically, pulmonary congestion and edema of the lungs appear as symmetrical, irregular, and diffuse areas of increased density located centrally or basally. The changes occur as a result of the intra-alveolar edema and congestion and dilatation of the pulmonary blood vessels. Either of these processes may predominate. If the change is primarily due to intra-alveolar edema, the affected regions may appear nodular, simulating metastatic or inflammatory pulmonary lesions. If vascular congestion and dilatation predominate, a picture of generalized hypervascularization, not unlike that seen in uncomplicated left ventricular cardiac decompensation, is present. This condition must be differentiated roentgenographically from such widely dissimilar diseases as sarcoidosis, chronic miliary tuberculosis, cystic fibrosis of the pancreas, parenchymal inflammatory diseases, and neoplastic infiltration.

The histories of 3 patients in whom pulmonary congestion and edema complicated acute glomerulonephritis are presented. Hypervolemia is the main etiological factor in this complication in nephritis, and varying degrees of left ventricular failure rarely contribute to the final picture. The authors

emphasize that this complication can remain clinically silent and that it should be suspected and looked for in every case of nephritis, even in the absence of evidence of congestive heart failure. Return of renal function effects diuresis and clearing of the pulmonary edema. Fluid allowances must be kept minimal, covering only insensible losses plus urinary output during the period of oliguria.

Prognosis of Fetuses at 33 Weeks' Gestation in Rh-Sensitized Women Who Have Had Preceding Stillbirths. G. Biering, I. Kaiser and W. Krivit. Journal-Lancet 79:277-283 (June) 1959 [Minneapolis].

The prognosis for the fetuses of women who are Rh-sensitized and who have had a preceding stillbirth is known to be poor. Delivery at or before 35 weeks of gestation is one of the methods advocated as a means of reducing the mortality rate. Early termination of the contact with maternal antibodies has been considered as a method of preventing the erythroblastosis from progressing to severe hydrops and subsequent death in utero. The results obtained by early delivery have been difficult to analyze because of lack of true control series. This paper presents a retrospective study of the prognosis of fetuses alive at 33 weeks' gestation in Rh-sensitized women who had had preceding stillbirths. From 1945 to 1957, 119 liveborn infants and 21 fetal deaths in utero were recorded at the University of Minnesota Hospitals in Minneapolis. In the mothers of 12 of the 119 liveborn infants and in 13 of the 21 fetal deaths in utero, a history of prior stillbirths was obtained. Eleven of these 25 pregnancies resulted in a dead fetus in utero before the 33rd week. Among the remaining 14 fetuses, who were alive at the 33rd week, there were 2 stillbirths, 1 hydropic infant, and 2 neonatal deaths due to kernicterus; thus, the final survival rate was 9 of 14, or 64%. The present series and review of the literature indicate great variability of the effects of isoimmunization. It is suggested that controlled clinical studies are necessary if convincing evidence of the value of early interruption of pregnancy is to be obtained.

Novobiocin in the Treatment of Bacterial Bronchopneumonia in Nursing Infants. L. Francalancia. Riv. clin. pediat. 63:248-258 (March) 1959 (In Italian) [Florence, Italy].

A group of 81 hospitalized nurslings with bacterial bronchopneumonia, aged up to 14 months, received a therapy of novobiocin, supplemented with penicillin, streptomycin, and chloramphenicol. The bacteriological examination of the material obtained from the pharynxes of the patients revealed the presence of the following strains of bacteria: Staphylococcus pyogenes var. aureus alone in 15 infants or associated with Streptococcus, Diplococcus, and Blastomyces organisms in 14; Staph. pyogenes var. albus in 2; gram-positive Diplococcus organisms in 25; streptococci in 8, gram-positive coccobacilli in 5; and other pathogenic agents in 8. Cultures of Staph. pyogenes var. aureus, isolated from the material obtained for testing, were sensitive to novobiocin and to erythromycin, but they were scarcely, or not at all, responsive to other antibiotics.

Daily dosage of novobiocin varied from 200 mg., divided into 2 oral doses, or 100 mg., divided into 2 doses administered intravenously, up to 500 mg., divided into 3 oral doses, or 200 mg., divided into 2 doses administered intravenously. The therapy with novobiocin produced remission of bronchopneumonia in 75 patients (92.5%) and deterioration of the clinical picture in 6. Remission of bronchopneumonia on roentgenologic examination was obtained between 5 and 12 days after the therapy with novobiocin began. This study suggests further use of novobiocin, combined with other antibiotics, for the treatment of bacterial bronchopneumonia in nursing infants.

UROLOGY

Use of Isoniazid Para-aminosalicylate for the Treatment of Genitourinary Tuberculosis. J. Cibert and J. Barbier. Presse méd. 67:841-842 (April 25) 1959 (In French) [Paris].

Isoniazid para-aminosalicylate, known also as pasiniazide, was used for 2 years in the treatment of 44 patients with genitourinary tuberculosis at the urologic clinic of Lyons, France. Fourteen of the cases were genital tuberculosis, and 30 were renal tuberculosis. In the genital tuberculosis group, 11 patients had a rapid clinical cure after being treated for 3 months, the diagnosis having been verified in 3 cases by epididymectomy. The 30 patients with renal tuberculosis were divided into 2 groups: one group had been treated for a long time with other medication and then were given pasiniazide; the other group received pasiniazide combined with streptomycin. Four of the patients with renal tuberculosis were seen in an advanced stage; they had intense cystitis, massive pyuria, and gross morphologic and functional changes on urography. The disease of 11 patients with renal tuberculosis was less severe; they had unilateral limited lesions, integrally conserved renal function, and only moderate morphologic changes. Ten of these patients were cured, but the condition of one, a 65-year-old man, was aggravated despite 4 months of treatment with 120 Gm. of streptomycin. Cystitis persisted after nephrectomy in this patient, and only after 3 months of postoperative treatment with streptomycin and pasiniazide was it cured.

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Results of treatment with pasiniazide are comparable, if not superior, to those with other antituberculous agents. In the patients with renal tuberculosis, cure was regularly and rapidly obtained by using the combination of streptomycin and pasiniazide; later the cure remained stable with pasiniazide alone. In the patients with genital tuberculosis, good results that were rapid and sure were obtained with pasiniazide alone in the majority of cases. Failures were usually in those forms of genitourinary tuberculosis in which the antituberculous agents were generally ineffectual. In 4 cases, however, pasiniazide was well tolerated when aminosalicylic acid and isoniazid were not. Pasiniazide alone was generally used only in cases of genital tuberculosis, although 4 cured cases of renal tuberculosis in which it was used alone are cited. There were only 3 cases of digestive intolerance to the drug, and urinary tolerance was excellent. Nephritic colic appeared only in 2 patients who were receiving the combination of streptomycin and pasiniazide, but on withdrawal of streptomycin and continuation with pasiniazide alone the colic was cured.

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OPHTHALMOLOGY

The Syndrome of the Aortic Arch: Ocular Manifestations of "Pulseless Disease" and a Report of a Surgically Treated Case. R. L. Tour and W. Fletcher Hoyt. Am. J. Ophth. 47:35-48 (May) 1959 [Chicago].

Takayasu in 1908 first adequately described the ocular manifestations of what was later to be called the "aortic arch syndrome." In spite of the fact that the associated eye findings represent only one facet of a far more widespread pathological state, the entire disease complex has in recent years been referred to as "Takayasu's disease." The ophthalmological aspects of this syndrome are due to hypoxia of ocular tissue. Hypoxia is also manifest in other organs, such as the brain, which are dependent for their nourishment on the patency of the large vessels arising from the aortic arch. Occlusion of these vessels, whether partial or total, results in a relatively characteristic disease, its severity depending upon the degree of such obstruction. The authors list 12 different terms under which the syndrome has been described. They discuss its signs and symptoms and review the pertinent literature. They believe that the term "aortic arch syndrome" should be applied to this condition.

The visual symptomatology results from the greatly altered blood supply to the head. Since both common carotid arteries are occluded in the aortic arch syndrome, these patients experience transient loss of vision in one or both eyes. The retinal blood supply may be sufficiently low so that postural hypotension, resulting from a change from the reclining to the sitting position, will cause observable pulsation in the central retinal artery and segmentation of the blood column. Numerous other changes in the ocular structures occur as a direct result of chronic hypoxia. Early in the disease the fundus may appear normal, or there may be merely a few microaneurysms in the periphery of the retina. Dilatation of the veins with bead-like swellings are next noted, and finally arteriovenous communications appear which encircle the optic disk. Similar arteriovenous anastomoses are described in the conjunctiva, and attention has been called to the appearance of newly formed vessels running circumferentially at the root of the iris. The reduced blood flow to the ciliary body is also undoubtedly responsible for the greatly lowered intraocular pressure which commonly occurs as part of the syndrome. Late complications, occurring when the disease is well established, consist of cataract formation, optic atrophy, retinal detachment, retinitis proliferans, vitreous hemorrhage, and corneal opacification.

Syphilitic aortitis with or without aneurysm has been most commonly suspected as etiological in the aortic arch syndrome, but a nonspecific type of arteritis has also been suggested as a causal factor. The treatment should be directed toward the primary process. Antisyphilitic therapy is indicated if the serologic tests are positive, but little improvement can be expected after the great vessels of the aortic arch have become obstructed. It is hoped that the advances in vascular surgery will soon permit the radical reconstruction of the aortic arch. In this connection the authors present the case of a 50-year-old woman, who was successfully treated by surgical removal of obstructions in the major branches of the aortic arch. After the operation, ophthalmodynamometry provided dramatic evidence of the increase in retinal arterial pressure at a time when the carotid pulses could not be palpated because of neck dressings. The almost immediate rise of intraocular pressure from very low preoperative levels to almost normal was further evidence of the improved circulation to the head. The advances in cardiovascular surgery have greatly improved the prognosis of the aortic arch syndrome.

THERAPEUTICS

Observations on the Treatment of Pulmonary Tuberculosis with Sulfoniazid. M. Lucchesi. Minerva med. 50:1426-1433 (May 12) 1959 (In Italian) [Turin, Italy].

Sulfoniazid had a beneficial effect on 36 patients, some of whom were psychiatric patients, with active pulmonary tuberculosis. The drug, combined with 60 Gm. per day of an aminovitaminic sirup, was given for from 4 to 6 months in a daily dose of from 50 to 70 mg. per kilogram of body weight, divided into 3 equal subdoses. Some of the patients were given 50 Gm. per day of streptomycin, which was

injected twice a day at the beginning of the treatment, every other day during the second month, and then every 3 days during the third month of treatment. Patients with severe lesions were also given a prednisone preparation. Laboratory tests made at the beginning, during, and after the treatment showed no changes in the composition of the blood or in the liver and kidney functions. The values of the erythrocyte sedimentation rate were high in most of the patients during the first 3 or 4 weeks of the treatment; afterwards they declined slowly and became normal or close to normal.

Sulfoniazid was tolerated well by all the patients. The results, especially when a large dose was given, were better than those usually obtained with isoniazid. Sputum became negative in 26 patients, some of whom had derived no benefit from previous prolonged treatment with other drugs, including isoniazid. Sulfoniazid, like other antituberculous drugs, in some patients had a marked beneficial effect on the general and pulmonary conditions, but had no effect on the sputum. The author believes that this may be due to adaptation of the bacteria to the antibacterial agent and to the selection of resistant individuals in a sensitive population, as well as to the progressive loss of virulence of the resistant strains. That the drug did not come into an efficient contact with the bacteria is a less probable hypothesis.

The author believes that the beneficial effect of sulfoniazid is connected with its bacteriolytic and bacteriostatic effects; the organism is freed in a rapid and progressive manner from the direct and indirect (biological and dynamic) harmful effect of Koch's baccilli and of their toxins. The possibility of giving the patient large quantities of the drug several times a day and for long periods of time makes sulfoniazid a useful drug in the treatment of the tuberculous psychiatric patient or of any other tuberculous patient from whom it is hard to obtain collaboration.

Treatment of Diabetes with N-N-Dimethyl Diguanide (LA 6023). E. Azerad and J. Lubetzki. Presse méd. 67:765-767 (April 18) 1959 (In French) [Paris].

N-N-dimethyl diguanide (LA 6023) was administered orally to 88 hospitalized patients with diabetes mellitus, aged between 16 and 75 years. The initial daily dosage consisted of 2 or 3 Gm. of the drug, administered as 3 or 4 tablets. Subsequently the dosage was decreased from 1.5 Gm. down to 0.5 Gm. a day. The results were good in 34 patients, fair in 35, and poor in 19. Younger patients responded better to the treatment than older ones. Obese patients with a mild variety of the disease benefited more from the treatment than did patients with a severe variety of the disease and with a tendency toward acidosis. Approximately one-half of the patients were receiving insulin treatment when the N-N-dimethyl diguanide treatment was instituted. It was possible to reduce, but not to eliminate entirely, the dosage of insulin in about two-thirds of the patients who received the combined treatment of insulin and N-N-dimethyl diguanide. The efficacy of N-N-dimethyl diguanide was weaker, the longer had been the preceding therapy with insulin. No severe side-effects to N-N-dimethyl diguanide developed. Moderate digestive disturbances, consisting mainly of nausea and diarrhea, were observed. Diarrhea induced discontinuation of the therapy in 4 patients.

PATHOLOGY

The Cytological Diagnosis of Solid Tumours by Small Needle Aspiration and Its Influence on Cancer Clinic Practice. I. H. Smith, J. H. Fisher, J. S. Lott and D. H. Thomson. Canad. M. A. J. 80:855-861 (June 1) 1959 [Toronto].

For some 20 years the Ontario Cancer Foundation's London Clinic, in conjunction with the department of pathology of the University of Western Ontario, has been studying the value of tumor aspirates as interpreted histologically from cut sections. A supplementary smear from the same material was occasionally made. At times from necessity when tissue fluid alone was obtained, or when the tumor proved to be cystic, the smear technique was used by itself. Gradually, and in particular since 1954, the curiosity of the authors has been replaced by the realization that the cytological interpretation of tumor aspirates has established itself as a most valuable procedure—surpassing and replacing the study of the sectioned aspirate in some instances and equalling it in others. Reliance is now placed on cytology to the extent that, when an aspiration is performed on an accessible lump, emphasis is placed first on obtaining tissue fluid for cytology, the plug forming a very important but secondary component of the procedure when and if procured.

The aspiration set consists of a 50-cc. Luer-Lok syringe, 20-gauge and 22-gauge needles of various lengths, and freshly prepared slides coated with egg albumin. The overlying skin is sterilized. If the no. 22 needle is routinely used, no local anesthetic is required. The tumor is immobilized with the left hand, and the needle is inserted until the tumor or its capsule is engaged. Maximum suction is employed, and the needle is guided through the tumor in 2 or 3 directions. When withdrawn, the tissue fluid within the needle is expressed on to the albuminized slides, 2 preparations being made. The material is smeared evenly by using the needle and, while the smear is still moist, the slides are immersed in fixative in a Coplin jar. Should a plug or excess tissue be available, it is placed in fixative for

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histological section. The smear is fixed for 15 minutes to one hour in fluid containing 1% glacial acetic acid in 95% ethyl alcohol. After fixation, and while still wet, it is stained with hematoxylin and eosin; it is then mounted and ready for microscopic examination.

The accuracy and clinical value of aspiration cytology has been appraised in 203 cases of cancer and 194 cases of deep-seated benign disease. A total of 524 smears was made. Exfoliative cytology and the cytology of effusions are not included in this study. In breast cancer 93% were confirmed cytologically, although in 18% more than one aspiration was required. Establishing diagnosis by this method permits a planned therapeutic approach and eliminates the need for frozen section examination in most instances. In lymph nodes secondarily involved by malignant disease, 94% of diagnoses were confirmed by aspiration cytology. There were 5 false-positive results (2.5%) in 194 benign cases; if interpreted in the light of clinical impression, this need be of little consequence. Of 203 malignant cases, 18 (8.8%) gave a false-negative result. Eight of the 18 were in breast lesions and required further histological investigation.

The simplicity, accuracy, and practical value of aspiration smear cytology for the solid tumor are established. The method deserves wider application. Although smear diagnosis of primary lymph node cancer is possible, it is still advisable to make the diagnosis histologically. No attempt was made to evaluate the accuracy of cytological smear examinations in benign diseases of the breast, but the authors feel that the psychological effect of establishing the diagnosis of cystic disease at once is most rewarding.

Hematomorphologic Determination of Sex: Determination of Sex from the Blood Picture. J. M. Caliezi. Schweiz. med. Wchnschr. **89**:499-503 (May 9) 1959 (In German) [Basel, Switzerland].

All cytological methods of determining sex are based on a morphologic peculiarity of the cellular nucleus in females. The hematomorphologic method, the only one the author is concerned with in this paper, takes a special position in so far as the sex characteristic—a chromatin attachment of the cellular nucleus—differs greatly from that of the other body cells, in form as well as in percentage of occurrence and, moreover, numerous secondary forms of nuclear attachments may cause confusion. The author points out that Davidson and Smith, the discoverers of hematological sex differentiation, demanded that in order to identify a person as "female" it should be possible to detect among 500 mature neutrophil leukocytes 6 specifically female nuclear attachments, which they designated as "drumsticks." The absence of drumsticks was evidence that the individual was "male," that is, the diagnosis was made by exclusion. In this connection the present author asks, "What about the blood smears that show 5 or less drumsticks?"

Other investigators found that the typically female nuclear attachment is found in men on rare occasions, whereas still others denied this, pointing out that these attachments were only similar to, but not identical with, drumsticks. Although on the basis of his own observations the author accepts this last view, he points out that differentiation of these atypical forms from the female nuclear drumstick attachment is very difficult and in some cases impossible. He describes and illustrates drumsticks, clubs, bulbs (or sessile nodules) and also mentions pseudodrumsticks or small clubs, tags, and minor lobes. He established the percentage incidence of the various nuclear attachments in 65 females and 35 males.

He regards as definitely "female" a blood smear containing 3 specifically female nuclear appendages in 500 mature neutrophils. Drumsticks and clubs are specifically female nuclear attachments, and sessile nodules and the scanty occurrence of tags are indications of female sex. A blood smear containing no specific female nuclear appendages in 300 mature neutrophil leukocytes definitely can be considered as indicative of the male sex, and the frequent occurrence of tags and the absence of sessile nodules are indications of the male sex.

PUBLIC HEALTH

Tuberculosis in Medical Students at the University of Maryland. J. R. Karns. Am. Rev. Tuberc. **79**:746-755 (June) 1959 [New York].

A tuberculosis control program was carried out on 2,302 medical students at the University of Maryland School of Medicine from 1934 to 1957. Only those who were observed for at least 1 year were included in this study. The survey showed that clinically significant tuberculosis had developed in 17 students while in school. The most striking feature was that in 16 of these the disease was diagnosed in the period from 1934 to 1950, whereas only 1 case occurred after 1950, indicating that the risk of tuberculous infection in the medical school has diminished in recent years. The reduction in morbidity has occurred without the use of BCG vaccine; it was brought about by early diagnosis, by spontaneous and improved treatment of tuberculosis as a contagious disease. Vollmer's test was positive in all students with clinically proved tuberculosis at the time of diagnosis. In a group of 53 students the patch test was found to be as accurate as the first-strength purified protein derivative (PPD). Since medical students are more exposed to the risk of tuberculous infection than any other student group, continuous vigilance is, therefore, necessary.

BOOK REVIEWS

Physiology of Cardiac Surgery: Hypothermia, Extracorporeal Circulation and Extracorporeal Cooling. By Frank Gollan, M.D., Assistant Director of Professional Services for Research, Veterans Administration Hospital, Nashville. Beaumont Lecture, Wayne County Medical Society. Cloth. $4.50. Pp. 96, with 18 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This monograph, a brief survey of some new techniques applied in cardiac surgery, is focused primarily on selected basic physiological and biochemical problems; it also discusses some current controversies and possible areas for future investigation. The presentation, in general, is somewhat cursory, but there is an extensive and interesting section dealing with the role of combined extracorporeal cooling and circulation techniques in cardiac surgery. The style is highly personal and flavored with many quotations from Coleridge, Einstein, Shakespeare, and others. This monograph has a useful bibliography. It is valuable as an interpretative essay which discusses present problems and applications in this field from a historical perspective.

Abnormal Haemoglobins: A Symposium Organized by the Council for International Organizations of Medical Sciences, Established under the Joint Auspices of UNESCO and WHO. Edited by J. H. P. Jonxis and J. F. Delafresnaye. Cloth. $9.50. Pp. 427, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

The symposium here reported took place in Istanbul under the auspices of a group of 50 international voluntary associations of specialists belonging to all the medical disciplines. The 26 papers, by different authors, with discussions, cover genetic and physical factors in the heterogeneity of hemoglobins, their identification and interpretation, clinical aspects, the hemoglobins in children and in different diseases, and the geographical distribution of different hemoglobins. Two papers deal with paper electrophoresis and serologic differentiation. An extensive bibliography is given, as well as a helpful index. The material is highly technical and presupposes a thorough knowledge of genetics, with an understanding of the exact meaning and true significance of such words as "genes," "alleles," "dimerization," "phanerosis," and "a propositus for the sibship." One should also have a working knowledge of electrophoretic, chromatographic, and salting-out techniques to understand the many figures in the text. The book contains a tremendous amount of data and should be extremely valuable to those working in the field of hemoglobins.

Current Problems in Allergy and Immunology. Papers dedicated to Béla Schick on occasion of his 80th birthday. Edited by William Kaufman. Cloth. $14.40; 60 Swiss francs. Pp. 992, with illustrations. S. Karger AG., Arnold Böcklinstrasse 25, Basel, Switzerland; Swiss Bank Corporation, New York, 1959.

This volume is composed of the articles published in four volumes of *International Archives of Allergy and Applied Immunology*. There are many excellent contributions in this book by masters of their subjects, mainly in the form of summations of material already published. Among the outstanding contributions are the papers on a comparison of fluorescein and radioactive iodine (I^{131}) as labels for antibodies, on the nature of tumor antigen, on the fate of labeled foreign antigens, on the immunological basis of carcinogenesis, on passive cutaneous anaphylaxis, on immunohematological disorders, on drug reactions, on the pathology of allergy, and on serologic reactions in rheumatoid arthritis. There are other good papers but, since there are more than 60 altogether, they cannot all be discussed or mentioned. Unfortunately, the good contributions are diluted by a number of mediocre or even poor and faddish expositions. This is the great weakness of the book and especially disturbing since such articles are given a stamp of respectability and authority when placed side by side with the works of truly great scientists. This is apt to mislead the uninformed reader. This volume, therefore, can be recommended only to those who already possess a good, discriminative acquaintance with the field.

Services to Blind Children in New York State. By William M. Cruickshank and Matthew J. Trippe. Syracuse University special education and rehabilitation monograph series 4. William M. Cruickshank, editor. [Brewster House book.] Cloth. $5. Pp. 495, with illustrations. Syracuse University Press, University Station, Box 87, Syracuse 10, New York, 1959.

This volume presents the results of a major study by the Syracuse University Research Institute. The stimulus for the study was the increased number of children blinded, particularly from retrolental fibroplasia. In New York state in 1956, there were 2,286 such persons under 21 years of age, and there was a probable total of 30,200 blind children in the United States. The principal objectives of the study were to determine the educational, social, and

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

health characteristics of the blind children in the state of New York, to determine the services available and used, to determine the nature of the programs offered by specialized and nonspecialized agencies for blind children, to study legislation, and to indicate areas of service to blind children.

It comes as a surprise to learn how inadequate the statistics are concerning blindness. In New York state only 33% of the children for whom annual visual appraisal was indicated had been examined within the year. This seems to be a particularly serious omission in the instance of 565 children with a diagnosis of "presumed blindness," of whom only 84 had been evaluated visually during the previous 12 months. The many physicians participating in local school board activities should find the following statement relevant: "The education of blind children with sighted children involves more, however, than a mere administrative decision. Blind children, wherever they are educated, must have programs equal to and exceeding those provided to sighted children. The public school administrator who decides to integrate blind children in the system must understand the implications of his decision in terms of personnel, equipment, orientation of general educators and other factors vital and essential to a satisfactory program." The importance of this statement is emphasized by the data which suggest that the residential school provides a more satisfactory education than the local school. The educational advantages of the residential school, however, must be weighed with other evidence which indicates that a more satisfactory emotional development occurs in the home environment.

The recommendations of this study for meeting the challenge of the blind child are, no doubt, applicable in a number of other states. The physician whose work brings him into contact with the blind should be particularly interested in this study of New York state and particularly with comparing the facilities offered by his own state.

Air Pollution Control. By W. L. Faith, Managing Director, Air Pollution Foundation, San Marino, California. Cloth. $8.50. Pp. 259, with illustrations. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16; Chapman & Hall, Ltd., 37-39 Essex St., Strand, London, W. C. 2, England, 1959.

This book was prepared to provide the nonspecialist with a better understanding of the nature and problem of air pollution and present basic facts that must be considered in air pollution control programs. The introductory chapter defines air pollution and contains brief summaries of its effects on health, property, and vegetation. The author then discusses the effects of meteorological conditions on the distribution of air contaminants and the application of meteorology to air pollution control. The bulk of the subject matter is concerned with the technical, chemical, and engineering aspects of control under the following classifications: dusts, fumes, and mists; gases; and odors and automobile exhausts. In these sections there is information on chemical composition and physical properties of contaminants, sources of contamination, sampling and analysis techniques, equipment, and abatement methods.

Concluding chapters discuss the planning and requirements of air pollution surveys and legal aspects in the control of air pollution. An extensive bibliography is provided at the end of each chapter and there are numerous diagrams, tables, graphs, and photographs throughout the book. The author has made an authoritative, concise, easily understood presentation of an exceedingly complex subject. This text should be an excellent nontechnical reference source for basic information about the important aspects of air pollution.

Hereditary Transient Paralysis with Special Reference to the Metabolism of Potassium: Familial Periodic Paralysis, Familial Episodic Adynamia. By Uffe Sagild. [Thesis, M.D., University of Copenhagen.] Paper. Pp. 242, with illustrations. Einar Munksgaard, Nørregade 6, Copenhagen, K, Denmark, 1959.

Recent work on electrolyte balance has focused attention on potassium, the element which is of central interest in the present book. Of the two types of muscular weakness he describes, one can be induced by giving potassium chloride. The other, when it occurs, is remedied by the same drug. The value of this book lies mainly in the numerous chemical determinations of the potassium content of the blood and urine and in the application of tracer techniques (by means of radioactive potassium [K^{42}]) to determine the amount of exchangeable potassium and the rate of exchange between injected K^{42} and body potassium. In addition there has been an extensive investigation of the genetic background of the author's patients, so that in one instance it was discovered that two apparently distinct pedigrees were linked more than 200 years ago. Patients temporarily paralyzed by hypopotassemia have been falsely accused of malingering. Others, knowing their family history, have occasionally induced attacks for the purpose of malingering. To his own collection of cases of transient paralysis from Denmark and Sweden the author adds the information available from the more than 700 cases reported in the literature, and the book closes with a good bibliography and an index.

It seems desirable to comment on the unhappy choice of terms to designate the two conditions studied and on the state of medical logic as here illustrated. The differential diagnosis between "familial episodic adynamia" and "familial periodic paralysis" is given in tabular form on page 134. The critical reader cannot help but observe that if a spell of moderate muscular weakness lasting a few hours were to occur at any time of the day in a boy at the age of 10 years, even a

study of his reflexes, his electromyogram, his electrical excitability, and the distribution of paralysis might not suffice to decide which condition he has and whether the administration of potassium on the basis of history and physical findings alone would prove lifesaving or fatal. The author asserts, on page 133, that the sole similarity between the two "diseases" is that both are "characterized by transient attacks of muscular weakness." His tabulation does not bear this out. The ultimate criteria are the chemical determinations of serum potassium and the patient's responses to administration of dextrose or potassium.

The conscientious student, likewise, must be confused by the words "episodic" and "periodic," which are used as antonyms. In reality neither of the conditions is periodic in the sense of recurring at regular intervals, and certainly there is nothing periodic about a single attack occurring in a man at the age of 70 years (page 188). The student will be further confused by the apparent distinction between paralysis and adynamia, which is hardly justified either by usage or by etymology. The habit of assigning arbitrary and unpredictable meanings to words and of implying distinctions where none are justified has long been an obstacle to clear thinking in medicine. It is to be hoped that a rational terminology for these two syndromes will be developed soon.

Atlas of Roentgenographic Measurement. By Lee B. Lusted, M.D., Associate Professor of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, New York, and Theodore E. Keats, M.D., Professor of Radiology, University of Missouri School of Medicine, Columbia. Cloth. $9. Pp. 176, with 119 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1959.

For years busily practicing radiologists have surrounded their film reading desks with framed or mounted illustrations, diagrams, and tables to which they could refer for specific information regarding the size, position, and other characteristics of various anatomic structures. The same practice has been followed by colleagues in other specialties who depend heavily on radiologic evidence in their work. A great service has been provided to both groups through the publication in one volume of some 56 classified groups of radiologic measurements for rapid and accurate reference.

After a wisely included consideration of the distortion factor to be expected when analyzing roentgenograms, the subject matter has been divided into nine anatomic categories, the largest of which deals with the skeletal system. All types of measurement (the location of the pineal body, the time of appearance of various skeletal ossification centers, the size of the heart, the length and caliber of the common bile duct, and the estimation of fetal age on the basis of bone length) are presented in a carefully standardized format. This includes a terse description of the essential examination technique, simple expression of the numerical values involved, and the source of the specific data. Illustrative material from original sources has been augmented extensively by excellent drawings. The book has been so bound that it remains open at any desired point when lying flat. This is a helpful feature when evidence from films is being compared directly with recorded values in the atlas.

The authors have used excellent judgment in selecting the source material to be included. It would have been good, however, to have had other meritorious sources of measurement data included as references by title only, for in several instances material that has been used is deeply interwoven with other published work whose authors have contributed importantly to the subject.

Cholera. By R. Pollitzer, M.D. With chapter on world incidence written in collaboration with S. Swaroop, Ph.D., M.P.H., Chief, Statistical Studies Section, World Health Organization. And chapter on problems in immunology and an annex written in collaboration with W. Burrows, M.D., Professor of Microbiology, University of Chicago, Chicago. World Health Organization monograph series no. 43. Cloth. £ 5; $20; 60 Swiss francs. Pp. 1019, with illustrations. World Health Organization, Palais des nations, Geneva, Switzerland; Columbia University Press, International Documents Service, 2960 Broadway, New York 27, 1959.

The author of this volume has brought together 1,000 pages of up-to-date information on cholera. The 11 listed chapters were printed as separate articles in the *Bulletin of the World Health Organization* prior to this revision. The effects of cholera on a person, population, community, state, nation, and international affairs and all phases of patient medical care, disease control, and prevention are adequately related in this book. Cholera, which Hippocrates described as a disease entity, has been the cause of six pandemics, some of which extended to the United States, in the past century. Cholera was the cause of 1,000 deaths in Calcutta as recently as 1955.

Metabolic Disturbances in Clinical Medicine. Edited by G. A. Smart, B.Sc., M.D., F.R.C.P., Professor of Medicine, University of Durham, Durham. Cloth. $10. Pp. 358, with illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This book is well organized. The subjects covered are interrelated so that one may get the whole picture of the various electrolyte and endocrine problems concerned in a disease entity without jumping from one chapter to another. This book should be useful for the general practitioner as well as the specialist. Each chapter reviews the biochemical changes in the various disease states where there are coexisting metabolic disturbances. Emphasis is more on biochemical changes than endocrine dysfunctions. The illustrations are adequate. The references are excellent and up to date.

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QUESTIONS AND ANSWERS

STEROID THERAPY OF CANCER

TO THE EDITOR:—*A man, 64 years old, has been found to have pulmonary cancer with metastases to the kidneys and adrenals. Should he be given cortisone or its derivatives or any hormone product? These are expensive medicaments, and there is no hope of cure. Should he receive this medicament through public funds, or should some other less expensive treatment be given to keep him comfortable?*

Francis J. Petrone, M.D., Fall River, Mass.

ANSWER.—There are no specific indications for the use of cortisone or its derivatives in treatment of patients with carcinoma of the lung. In the patient under discussion, there are two possible indications for use of cortisone as palliative treatment. If the patient is suffering from adrenal insufficiency due to destruction of adrenal tissue by metastases, replacement doses of cortisone would give effective relief. Twenty-five milligrams of cortisone twice daily by mouth would correct the symptoms of adrenal insufficiency if the patient is not under any stress. A larger dosage should be used in a patient who is ill. Although metastases to the adrenal glands are quite common, complete destruction of the adrenal glands resulting in adrenal insufficiency is extremely rare. The diagnosis of adrenal insufficiency can be established by measurement of the blood or urine 17-hydroxycorticoids and by administration of ACTH to determine whether the adrenal glands can be stimulated.

The second possible indication for use of cortisone in patients with advanced cancer might be for relief of symptoms. There is no evidence to indicate that large doses of cortisone produce any significant inhibiting effect on the growth of the tumor. However, relief of pain and improvement in the sense of well-being and in appetite are not infrequently seen in patients in the terminal stages of cancer, unassociated with any inhibitory effects on the tumor itself. These effects of cortisone are usually short-lasting. The relief of symptoms and improvement in well-being may continue for several weeks and thus constitute worthwhile palliative therapy.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

"PASSING OUT" SPELLS

TO THE EDITOR:—*A 10-year-old girl has had "passing out" spells for the past two years. These at first lasted only a few seconds, but they now last up to half a minute. The child has no memory of the spells. Frequently there is incontinence of urine. Skull x-rays were normal. An electroencephalogram in 1957 revealed diffuse abnormal waves consistent with petit mal convulsive disorder and possibly grand mal variance. Trial therapy with diphenylhydantoin sodium resulted in aggravation of the symptoms. Large doses of vitamin B provided no results. This year the patient was seen by a neurosurgeon who verified the diagnosis of petit mal and prescribed methsuximide, 0.3-Gm. capsules, three times daily. This also appears to aggravate the symptoms, with development of more frequent attacks, considerable irritability, and behavior changes. At the age of about 5 years this child had recurrent fever up to 105 F (40.6 C) and was found to have a kidney and bladder infection. No source of this was ever discovered. She continues to have occasional evening fever of 99 to 100 F (37.2 to 37.8 C) but no urinary symptoms. There have been no operations, hospitalizations, or serious illnesses. Please advise as to diagnostic or therapeutic measures not yet used.*

George R. Farrell, M.D., San Diego, Calif.

ANSWER.—The urinary infection does not appear to be associated with the neurological problem. Although the febrile episodes may aggravate the convulsive disorder, they cannot be the cause of it. The description of the seizures is not that of major convulsions, since they last such a short time and are described primarily as loss of consciousness. Incontinence of urine does occasionally occur in minor seizures. It is more frequent in psychomotor seizures than it is in petit mal. There is no abnormal activity described in the period of loss of consciousness, and the electroencephalographic findings are more consistent with petit mal than with psychomotor seizures.

Also, the result of the therapeutic trials would suggest that this is not a psychomotor seizure, since diphenylhydantoin sodium might well be expected, in adequate doses, to reduce psychomotor seizures rather than to aggravate them. Indeed, aggravation of the symptoms by diphenylhydantoin suggests that these are petit mal, since this is a common occurrence. A therapeutic trial of trimethadione, be-

ginning with 0.3 Gm. per day and increasing to a maximum of 2.7 Gm. per day, if necessary, to control seizures might be indicated. This should be covered with a small amount of phenobarbital, ¼ grain (15 mg.) three times daily, so as to avoid the possibility of inducing major seizures by the use of trimethadione.

The electroencephalogram should be repeated—in the sleeping state as well as in the waking state. There is also the possibility that this child has a progressive degenerative disease, since irritability and behavior changes are developing. However, with the concern of the parents and the undoubted effect of the repeated seizures on the child, particularly if there is severe urinary incontinence, it is quite likely that the irritability and behavior changes are due to environmental pressures rather than to any progressive disease. If therapy with trimethadione is not effective, paramethadione should be tried, and if this also is not effective, then phensuximide.

PSORIASIS THERAPY

To the Editor:—*A lay magazine describes apparent improvement in psoriasis after aminopterin and methotrexate (A-methopterin) therapy. The rationale for such treatment does not seem readily apparent. Is there any basis for it?*

Charles E. Krause, M.D., Caldwell, Idaho.

Answer.—The rationale of the use of aminopterin or methotrexate in psoriasis is not too readily apparent. In psoriasis, it is believed that there is increased keratinization of the epidermal cells as well as increased water vapor loss. One of the effects of aminopterin and methotrexate is to inhibit epithelial proliferation. Both are potentially dangerous drugs and can produce serious toxic effects. These may be ulceration of the buccal mucosa, diarrhea, cramps, thinning of the hair, delayed wound healing, and depression of the number of leukocytes.

DIARRHEA AND LIVER DISEASE

To the Editor:—*For the past few years a woman has had a severe case of chronic diarrhea. There is some palmar erythema. A needle biopsy of the liver showed fatty infiltration and 30% retention of sulfobromophthalein. Are there any records of such liver findings in people past the age of 50 who have no symptoms of any liver disorder?*

B. G. Barentine, M.D., Laurel, Miss.

Answer.—Chronic diarrhea associated with fatty infiltration of the liver and a 30% sulfobromophthalein retention in a person over 50 years of age is suggestive of an intestinal disease with a secondary liver disorder. In order to give a reasonable reply to the above question, it would be necessary to know about the nature of the intestinal disorder causing the diarrhea. Regional enteritis, ulcerative colitis, or a neoplastic disease should naturally receive consideration. Sulfobromophthalein retention of the magnitude described usually indicates more than fatty infiltration of the liver. Such retention is most unlikely in patients with normal livers. More information than is available is needed for an adequate reply to the question.

CUTTING OF VAGUS NERVES AND DIZZY SPELLS

To the Editor:—*A 55-year-old physician underwent a gastrectomy six months ago; at the same time both vagus nerves were cut. During the last four weeks the patient has had recurrent attacks of dizzy spells with nystagmus, nausea, and vomiting. Results of the past-pointing test were positive. The attacks last from 1 to 10 hours. There is no tinnitus or hearing impairment. Could there be any relationship between the cutting of the vagus nerves and the "Ménière-like" attacks?*

Joseph Berberich, M.D., New York.

Answer.—If both vagus nerves are severed (it is doubtful that both were completely severed) there is no feed-back efferently, so, although a branch of the vagus nerve goes to the labyrinth, this should not be the cause of the patient's symptoms. It is more probable that medication postoperatively or the original anesthetic is the cause of the vertigo and nystagmus. It is also conceivable that neurological examination might prove that this patient has Ménière's syndrome, multiple sclerosis, or other neurological disease superimposed on the original condition. This patient should have a neurological survey.

TREATMENT OF SYPHILIS

To the Editor:—*What is the proper oral dosage of penicillin in treating various forms of syphilis? Are the "mycin" drugs any better?*

Arthur F. Edwards, M.D., Los Angeles.

Answer.—I can see no indication for the oral administration of penicillin in the treatment of syphilis. The dosage schedule for injectable penicillin is so well established and the drug is so inexpensive that it would seem pointless to use penicillin orally. In fact, I know of no series of cases reported in the literature in which it has been so used in the treatment of syphilis.

The broad-spectrum antibiotics are nearly all effective in the treatment of syphilis. This has been definitely demonstrated, first with oxytetracycline, and at present tetracycline would certainly be just as effective. One gram a day for from 10 to 20 days should be adequate therapy in most cases. Probably more prolonged administration and higher dosage would be necessary for active general pare-

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sis or tabes dorsalis, but these cases today are rare. If medication must be by the oral route, tetracycline reactions, in all probability, would be far less in number and in degree than those possibly encountered with orally given penicillin.

DRIED LIPS

To the Editor:—*A 60-year-old man for 20 years has had drying and cracking of his lower lip. He does not smoke. For the past 10 years he has had artificial dentures. Recently he has had a small malignant growth removed from a corner of the lower lip by radiation therapy. The lower lip is still dry and cracked. Is the origin of this condition known? Is there any therapy?*

M.D., Florida.

Answer.—The query is from a physician in Florida, and presumably the patient has lived there for many years. In this case, dryness of the lower lip is probably due to prolonged exposure to the intense Floridian actinic radiations. The cancer of his lip might also be due in part to the sun's rays. When he is outdoors, his lips should be protected with a sun-screening agent in an emollient base. There are many such products on the market. A person with cheilitis of long standing, with fissures, and especially with a history of an epithelioma, should be examined closely for evidence of other cancerous growths. In some cases it is advisable to have a "stripping operation" of the lip to prevent further trouble. Consultation with a dermatologist or with a head-and-neck surgeon is advisable.

PENICILLIN ALLERGY

To the Editor:—*In the* Southern Medical Journal, *February, 1959, page 186, there is a convincing article on immediate reactions to penicillin. The question has been brought up in staff meeting as to whether scratch tests to detect penicillin allergy might be a cause of promoting allergic responses to the drug. Also, since the form most commonly given is procaine penicillin, would it be necessary to skin test with this, or can one state whether a reaction would be due to the procaine or to the penicillin? We would appreciate advice in this matter from an allergist and an opinion of the medicolegal factors involved in testing for penicillin sensitivity before giving injections.*

Ward B. Breidenthal, M.D., Banner Elk, N. C.

Answer.—There is no evidence from either experience with penicillin or the use of other allergens that scratch tests predispose to an increase in incidence of allergy. Since an immediate type of allergic reaction to procaine is rare (a few equivocal reports of such reactions have been made), one can safely assume that an allergic reaction after administration of procaine penicillin is due to penicillin sensitivity.

The last part of the inquirer's final sentence is unclear. Presumably he wishes to know what the medicolegal responsibility is if the patient is not tested for sensitivity to penicillin and has a severe reaction after its administration. As an allergist who is not an authority on medicolegal aspects of such a case, this consultant would venture the opinion that a thorough inquiry concerning previous reactions to penicillin is more important than skin tests with the substance. A patient who gives a history of previous reactions should be tested by skin and ophthalmic tests if penicillin administration is urgent. Since the value of skin tests in determining the likelihood of systemic reactions is in controversy, this consultant doubts legal liability if no skin test was done, providing that a reliable history indicates that the patient has never received penicillin or that he has never had reactions from its administration.

SUDAN RED TEST FOR FAT

To the Editor:—*Please give information about the Sudan red test for detection of fat in the urine. On two occasions, elderly patients operated on for hip prosthesis have died with what looked like embolic phenomena. Autopsies did not show any cause of death. We are trying to work out a laboratory test that will help to determine whether fat emboli may have occurred.*

Thornton Kell, M.D., Ardmore, Okla.

Answer.—Various azo dyes, including Sudan 2, 3, and 4, have been used as stains for fat. Their ability to stain fat depends on their solubility in oil, and they probably color by means of a physical process. Of the Sudan compounds, Sudan 4 probably is the best for this purpose. It is customarily used as Herxheimer's solution, which consists of 1 Gm. of Sudan 4 dissolved in a mixture of 50 ml. of 70% alcohol and 50 ml. of acetone. When urine is to be stained, a drop of urine is placed on the slide, care being taken to skim the specimen off the surface of the collected urine. An equal amount of Herxheimer's solution is added and the specimen examined under the microscope.

Normal urine does not contain fat, but because fat is found in the urine under a variety of conditions, it is unlikely that a test of this nature will be reliable in determining the presence or absence of fat emboli. Usually, when fat emboli are present in the body, they are found in the lungs. One must be careful to distinguish between fat within and outside of the capillaries, the latter being found normally. Herxheimer's solution may be used in this process of detection. It is important that the tissue never be exposed to alcohol of more than 70% concentration and that all other fat solvents,

such as xylene and pure acetone, be avoided. Such tissues usually are fixed in formaldehyde and frozen sections prepared. After these have been placed in 70% alcohol, they are stained with Herxheimer's solution. Slides are mounted in glycerol.

PARONYCHIA OF FUNGOUS ORIGIN

To the Editor:—*Please give an opinion on how best to treat a fingernail which has transverse ridges with other irregularities and pockmarks in the nail and with a raised, rolled area of the skin at the base of the nail, slightly red and slightly painful but never approaching the redness, the pain, or the appearance of acute paronychia.*

J. T. Phillips, M.D., Norton, Va.

Answer.—This nail dyscrasia fits into the clinical picture of paronychia due to the fungus Candida albicans (yeast infection). To confirm this clinical opinion, microscopic examination should be performed. Many of these infections respond to a solution containing 5% nystatin or 8% sodium caprylate. The patient must keep the area out of water and avoid contact with raw fruits and vegetables. Oral administration of nystatin can be used. It is presumed that the possibility of diabetes has been investigated.

STEROID LEVELS IN CHILDREN

To the Editor:—*What are the normal values for 17-ketosteroid and 17-hydroxycorticosteroid determinations in children according to the more popular methods of these determinations?*

G. C. Haskell, M.D., Springfield, Ohio.

Answer.—The plasma 17-ketosteroid level in normal adult men and women averages 60 mcg. per 100 ml. In the newborn infant, the level is equal to or higher than that of the normal adult during the first day of life and falls to low levels by the end of the first week. During infancy and childhood, plasma 17-ketosteroids are practically absent until the onset of puberty, the concentration remaining below 2 mg. until the 8th year. In adult females urinary excretion is between 5 and 14 mg., with an average of 9 mg. in 24 hours; for adult males it is 8 to 22 mg., with an average of 14 mg. The urinary output from the 10 to the 14th day of life is 1.2 to 2.5 mg. per 24 hours and falls to 0.5 mg. by the third to fourth week. There is little change until the 8th year, when there is a gradual rise from approximately 2 mg. to 8 mg. by the 15th year (Wilkins: Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1957, p. 306).

The plasma 17-hydroxycorticosteroid level in normal healthy adults varies between 4 and 10 mcg. per 100 ml., and the urinary output, from 3 to 9.3 mg. per 24 hours (Nelson and associates: *J. Clin. Endocrinol.* 11:1021, 1951). In 40 normal children Ely and co-workers (*Pediatrics* 13:403, 1954) found the mean plasma value to be 12.0 and the standard error of the mean ± 1.29 mcg. per 100 ml., a range of 0 to 28.7 mcg. Klein and others (*J. Pediat.* 43:385, 1953) found the mean free corticoid level in children to be 13 mcg., with a standard error of the mean of ± 1.21. After birth, the 17-hydroxycorticosteroid level of the infant's plasma falls to low levels by the third day and then rises to adult levels within 7 to 14 days.

USE OF OLD-FAVORITE REMEDY

To the Editor:—*Use of elixir of iron, quinine, and strychnine, prescribed in our hospital for a number of years, is being challenged by our clinical director, who states that it is outmoded and that newer drugs are better. Several staff members disagree. Its general tonic effect is well known, and I feel, from years of experience, that it does something for the tired-out patient who also has hypertension, especially middle-aged and older persons. It makes them feel better and eat better, and for some reason they lose that tired and always-sleepy feeling. The blood pressure effect is admittedly mild.*

Alfred W. Andreasen, M.D., Danville, Ky.

Answer.—Elixir of iron, quinine, and strychnine has a long clinical history, with wide confirmation of its value as a "tonic." Elixirs and tonics, however, are no longer fashionable in the American hard-driving, highly commercialized therapeutics market; reference to them is found only in European pharmacology textbooks. K. O. Møller, in the most recent edition of his widely used "Pharmakologie als theoretische Grundlage einer rationellen Pharmacotherapie" (New York, Grune & Stratton, Inc., 1947) fully describes the significant therapeutic indications for strychnine as a tonic. Bitterness of both quinine and strychnine even in the flavored elixir is enough to give a stimulus to appetite. Strychnine does facilitate ganglionic nerve transmission. Quinine has wide effects, often helping to stabilize cellular function, particularly with reference to water and electrolyte balance. It is well known that iron is useful in chronic debilitating conditions, particularly where iron deficiency may be part of a picture of anemia.

It would seem that the tried and tested tonic value of elixir of iron, quinine, and strychnine deserves continued recognition. Its effects are not dramatically quick as in the case of many new drugs which seem to have a stimulating effect on the central nervous system, but it does improve the over-all condition in tired middle-aged or older persons, in patients convalescing from debilitating disease, and in conditions where there is a let-down feeling or mild depression.

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